10/813,384

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/34, 31/36, 31/38, 31/39, 31/41, 31/415, 31/425, 31/445, 31/505, 31/535, C07D 215/14, 231/12, 263/32, 277/10, 277/66, 285/06, 307/80, 317/50, 319/20, 333/78, 401/12, 409/04, 495/02

A1

(11) International Publication Number: **WO 99/66925**

(43) International Publication Date: 29 December 1999 (29.12.99)

(21) International Application Number: PCT/US99/14561

(22) International Filing Date: 24 June 1999 (24.06.99)

(30) Priority Data:
60/090,493 24 June 1998 (24.06.98) US

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HALBERT, Stacie, Marie [US/US]; 149 Montgomery Drive, Harleysville, PA 19438 (US). MICHAUD, Evelyne [FR/FR]; 5, rue Georges Citerne, F-45015 Paris (FR). THOMPSON, Scott, Kevin [US/US]; 75 Guilford Circle, Phoenixville, PA 19460 (US). VEBER, Daniel, Frank [US/US]; 290 Batleson Road, Ambler, PA 19002 (US).

(74) Agents: STERCHO, Yuriy, P. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PROTEASE INHIBITORS

(57) Abstract

The present invention provides diacyl hydrazine compounds, and pharmaceutically acceptable salts, hydrates and solvates thereof, which inhibit proteases, including cathepsin K, pharmaceutical compositions of such compounds, novel intermediates of such compounds, and methods for treating diseases of excessive bone loss or cartilage or matrix degradation, including osteoporosis; gingival disease including gingivitis and periodontitis; arthritis, more specifically, osteoarthritis and rheumatoid arthritis; Paget's disease; hypercalcemia of malignancy; and metabolic bone disease, comprising inhibiting said bone loss or excessive cartilage or matrix degradation by administering to a patient in need thereof a compound of the present invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14561

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/16433 A1 (SMITHKLINE BEECHAM CORPORATION) 09 May 1997. See the entire document especially pages 6-68.	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 AUGUST 1999	Date of mailing of the international search report 10 SEP 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer TAOFIQ A. SOLOLA JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14561

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/34, 31/36, 31/36, 31/38, 31/39, 31/41, 31/415, 31/425, 31/445, 31/505, 31/535; C07D 215/14, 231/12, 263/32, 277/10, 277/66, 285/06, 307/80, 317/50, 319/20, 333/78, 401/12, 409/04, 495/02

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/235.5, 236.6, 255, 259, 318, 363, 385, 439, 443, 444, 452, 465, 470, 472; 544/123, 324; 546/114, 153, 268.4; 548/127, 181, 190, 235, 364.1; 549/50, 58, 60, 350, 362, 434, 466, 476

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/235.5, 236.6, 255, 259, 318, 363, 385, 439, 443, 444, 452, 465, 470, 472; 544/123, 324; 546/114, 153, 268.4; 548/127, 181, 190, 235, 364.1; 549/50, 58, 60, 350, 362, 434, 466, 476

PROTEASE INHIBITORS

FIELD OF THE INVENTION

This invention relates in general to diacyl hydrazine protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly compounds which inhibit cysteine proteases, even more particularly compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly compounds which inhibit cysteine proteases of the cathepsin family, most particularly compounds which inhibit cathepsin K. Such compounds are particularly useful for treating diseases in which cysteine proteases are implicated, especially diseases of excessive bone or cartilage loss, e.g., osteoporosis, periodontitis, and arthritis.

BACKGROUND OF THE INVENTION

Cathepsins are a family of enzymes which are part of the papain superfamily of cysteine proteases. Cathepsins B, H, L, N and S have been described in the literature. Recently, cathepsin K polypeptide and the cDNA encoding such polypeptide were disclosed in U.S. Patent No. 5,501,969 (called cathepsin O therein). Cathepsin K has been recently expressed, purified, and characterized. Bossard, M. J., et al., (1996) *J. Biol. Chem.* 271, 12517-12524; Drake, F.H., et al., (1996) *J. Biol. Chem.* 271, 12511-12516; Bromme, D., et al., (1996) *J. Biol. Chem.* 271, 2126-2132.

Cathepsin K has been variously denoted as cathepsin O or cathepsin O2 in the literature. The designation cathepsin K is considered to be the more appropriate one.

Cathepsins function in the normal physiological process of protein degradation in animals, including humans, e.g., in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated as causative agents in various disease states, including but not limited to, infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and the like. *See* International Publication Number WO 94/04172, published on March 3, 1994, and references cited therein. *See also* European Patent Application EP 0 603 873 A1, and references cited therein. Two bacterial cysteine proteases from P. gingivallis, called

gingipains, have been implicated in the pathogenesis of gingivitis. Potempa, J., et al. (1994) *Perspectives in Drug Discovery and Design*, 2, 445-458.

Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I collagen represents the major structural protein of bone comprising approximately 90% of the protein matrix. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodelling at discrete foci throughout life. These foci, or remodelling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

Several published studies have demonstrated that inhibitors of cysteine proteases are effective at inhibiting osteoclast-mediated bone resorption, and indicate an essential role for a cysteine proteases in bone resorption. For example, Delaisse, *et al.*, *Biochem. J.*, 1980, *192*, 365, disclose a series of protease inhibitors in a mouse bone organ culture system and suggest that inhibitors of cysteine proteases (e.g., leupeptin, Z-Phe-Ala-CHN_2) prevent bone resorption, while serine protease inhibitors were ineffective. Delaisse, *et al.*, *Biochem. Biophys. Res. Commun.*, 1984, *125*, 441, disclose that E-64 and leupeptin are also effective at preventing bone resorption *in vivo*, as measured by acute changes in serum calcium in rats on calcium deficient diets. Lerner, *et al.*, *J. Bone Min. Res.*, 1992, *7*, 433, disclose that cystatin, an endogenous cysteine protease inhibitor, inhibits PTH stimulated bone resorption in mouse calvariae. Other studies, such as by Delaisse, *et al.*, *Bone*, 1987,

8, 305, Hill, *et al.*, *J. Cell. Biochem.*, 1994, *56*, 118, and Everts, *et al.*, *J. Cell. Physiol.*, 1992, *150*, 221, also report a correlation between inhibition of cysteine protease activity and bone resorption. Tezuka, *et al.*, *J. Biol. Chem.*, 1994, *269*, 1106, Inaoka, *et al.*, *Biochem. Biophys. Res. Commun.*, 1995, *206*, 89 and Shi, *et al.*, *FEBS Lett.*, 1995, *357*, 129 disclose that under normal conditions cathepsin K, a cysteine protease, is abundantly expressed in osteoclasts and may be the major cysteine protease present in these cells.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

Several cysteine protease inhibitors are known. Palmer, (1995) *J. Med. Chem.*, *38*, 3193, disclose certain vinyl sulfones which irreversibly inhibit cysteine proteases, such as the cathepsins B, L, S, O2 and cruzain. Other classes of compounds, such as aldehydes, nitriles, α-ketocarbonyl compounds, halomethyl ketones, diazomethyl ketones, (acyloxy)methyl ketones, ketomethylsulfonium salts and epoxy succinyl compounds have also been reported to inhibit cysteine proteases. *See* Palmer, *id*, and references cited therein.

U.S. Patent No. 4,518,528 discloses peptidyl fluoromethyl ketones as irreversible inhibitors of cysteine protease. Published International Patent Application No. WO 94/04172, and European Patent Application Nos. EP 0 525 420 A1, EP 0 603 873 A1, and EP 0 611 756 A2 describe alkoxymethyl and mercaptomethyl ketones which inhibit the cysteine proteases cathepsins B, H and L. International Patent Application No. PCT/US94/08868 and European Patent Application No. EP 0 623 592 A1 describe alkoxymethyl and mercaptomethyl ketones which inhibit the cysteine protease IL-1b convertase. Alkoxymethyl and mercaptomethyl ketones have also been described as inhibitors of the serine protease kininogenase (International Patent Application No. PCT/GB91/01479).

Azapeptides which are designed to deliver the azaamino acid to the active site of serine proteases, and which possess a good leaving group, are disclosed by Elmore *et al.*, *Biochem. J.*, 1968, *107*, 103, Garker *et al.*, *Biochem. J.*, 1974, *139*, 555, Gray *et al.*, *Tetrahedron*, 1977, *33*, 837, Gupton *et al.*, *J. Biol. Chem.*, 1984, *259*, 4279, Powers *et al.*, *J. Biol. Chem.*, 1984, *259*, 4288, and are known to inhibit serine proteases. In addition, Magrath *et al.*, *J. Med. Chem.*, 1992, *35*, 4279, Baggio *et al.*, Biochemistry, 1996, *35*, 3551 and Xing *et al.*, *J. Med. Chem.* 1998, 41, 1344 discloses certain azapeptide esters as cysteine protease inhibitors.

Diacyl carbohydrazides have recently been disclosed as inhibitors of cathepsin K by Thompson *et al.*, *Proc. Natl. Acad. Sci., U.S.A.*, 1997, *94*, 14249 and in International Patent Application No. WO 97/16433.

Antipain and leupeptin are described as reversible inhibitors of cysteine protease in McConnell et al., *J. Med. Chem.*, *33*, 86; and also have been disclosed as inhibitors of serine protease in Umezawa et al., 45 *Meth. Enzymol.* 678. E64 and its synthetic analogs are also well-known cysteine protease inhibitors (Barrett, *Biochem. J.*, *201*, 189, and Grinde, *Biochem. Biophys. Acta*, , *701*, 328).

Thus, a structurally diverse variety of cysteine protease inhibitors have been identified. However, these known inhibitors are not considered suitable for use as therapeutic agents in animals, especially humans, because they suffer from various shortcomings. These shortcomings include lack of selectivity, cytotoxicity, poor solubility, and overly rapid plasma clearance. A need therefore exists for methods of treating diseases caused by pathological levels of cysteine proteases, including cathepsins, especially cathepsin K, and for novel inhibitor compounds useful in such methods.

We have now discovered a novel class of diacyl carbohydrazide compounds which are protease inhibitors, most particularly of cathepsin K.

SUMMARY OF THE INVENTION

An object of the present invention is to provide diacyl hydrazine protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly such compounds which inhibit cysteine proteases, even more particularly such compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly such compounds which inhibit cysteine proteases of the cathepsin family, most particularly such compounds which inhibit cathepsin K, and which are useful for treating diseases which may be therapeutically modified by altering the activity of such proteases.

Accordingly, in the first aspect, this invention provides a compound according to Formula I.

In another aspect, this invention provides a pharmaceutical composition comprising a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient.

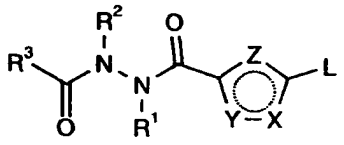
In yet another aspect, this invention provides intermediates useful in the preparation of the compounds of Formula I.

In still another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, most particularly cathepsin K.

In a particular aspect, the compounds of this invention are especially useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of Formula I:



I

wherein:

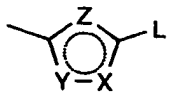
L is selected from the group consisting of:C_{2-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $CH(R^4)NR^5R^6$, $CH(R^4)Ar$, $CH(R^4)OAr'$, and NR^4R^7;

X, Y, Z are independently selected from the group consisting of: N, O, S and CR^{10}, provided that at least two of X, Y and Z are heteroatoms and at least one of X, Y and Z is N, or one of X, Y and Z is C=N, C=C or N=N and the other two are CR^{10} or N, provided that X, Y and Z together comprise at least two N;

-- indicates a single or double bond in the five-membered heterocycle;

R', R^1, R^2, R^5, R^{10}, R^{12}, R^{16} and R^{17} are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^3 is selected from the group consisting of: C_{3-6}alkyl, Ar, Het, $CH(R^{11})Ar$, $CH(R^{11})OAr$, $NR^{11}R^{12}$, $CH(R^{11})NR^{12}R^{13}$; and



;

R^4, R^{11}, and R^{15} are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-11}cycloalkyl-C_{0-6}-alkyl, Ar-C_{0-6}alkyl, Ar-C_{2-6}alkenyl, Ar-C_{2-6}alkynyl, Het-C_{0-6}alkyl, Het-C_{2-6}alkenyl, Het-C_{2-6}alkynyl, C_{1-6}alkyl, optionally substituted by OR^8, SR^8, NR^8R^9, $N(R')CO_2R'$, CO_2R', $CONR^{10}R^{11}$, and $N(C{=}NH)NH_2$;

R^6 and R^{13} are independently selected from the group consisting of: R^{14}, $R^{14}C(O)$, $R^{14}C(S)$, $R^{14}OC(O)$, and $R^{14}OC(O)NR^9CH(R^{15})(CO)$;

R^7 is selected from the group consisting of: C_{1-6}alkyl, C_{1-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}-alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^4 and R^7 may be combined to form a 3-7 membered monocyclic or 7-10-membered bicyclic carbocyclic or heterocyclic ring, optionally substituted with 1-4 of C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkoxy, Ar-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}NR^8R^9$, $O(CH_2)_{1-6}NR^8R^9$;

$R^8$and R^9 are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, and $R^{16}R^{17}NC_{2-6}$alkyl;

R^{14} is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

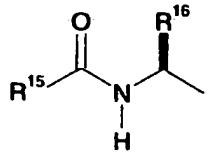
and pharmaceutically acceptable salts, hydrates and solvates thereof.

Compounds of Formula I wherein R^1 and R^2 are H are preferred.

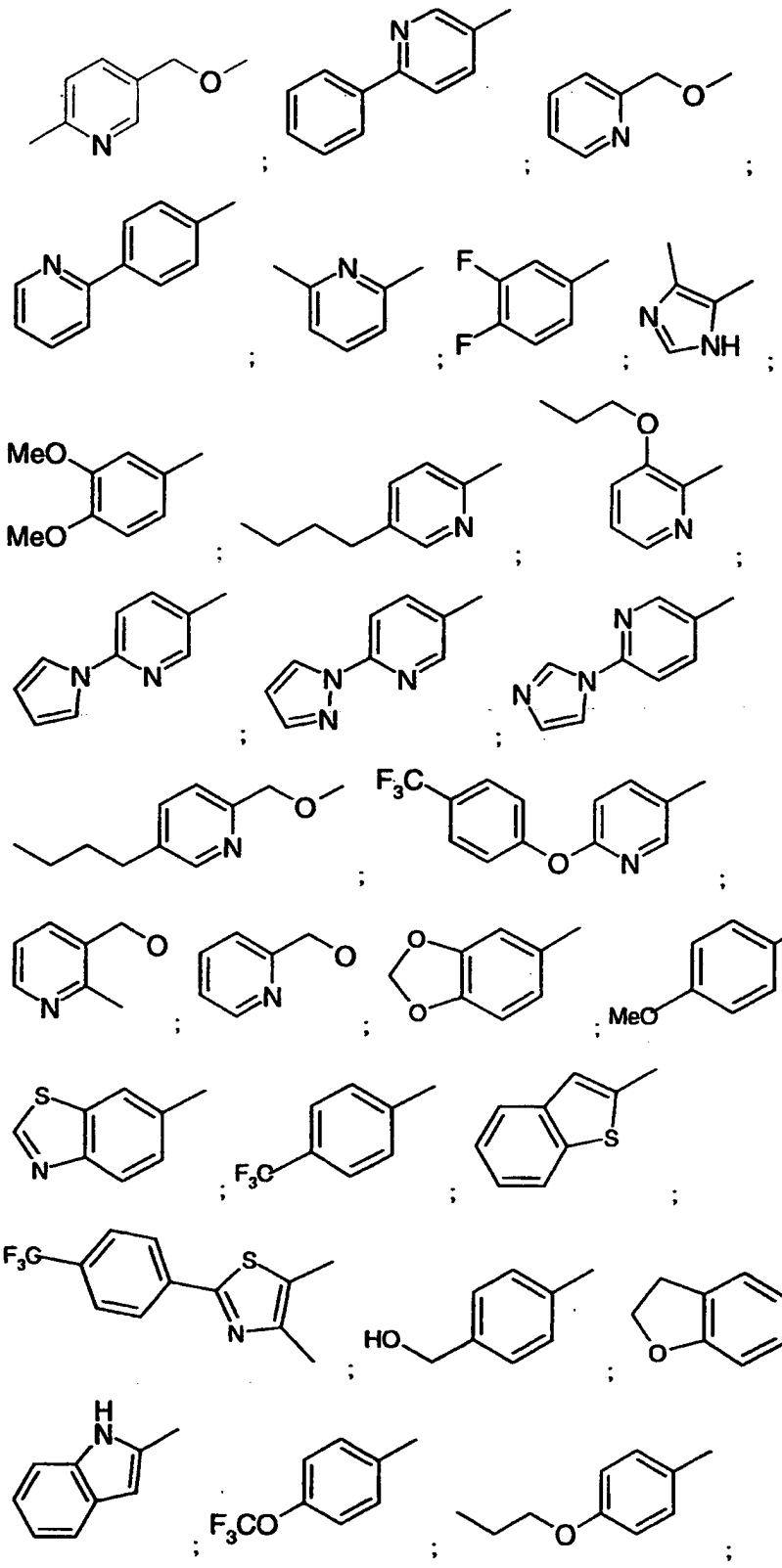
Also preferred are compounds of Formula I wherein X is S, Y is CH, and Z is N.

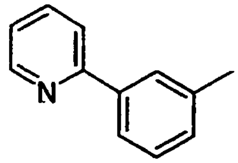
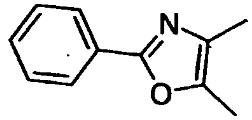
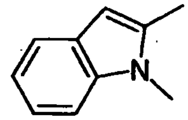
Also preferred are compounds of Formula I wherein:

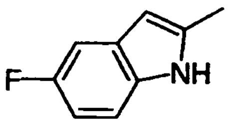
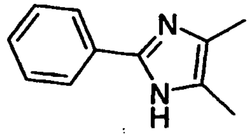
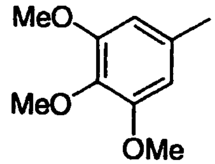
R^3 is preferably:

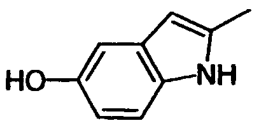
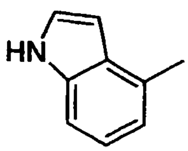
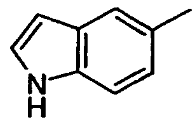


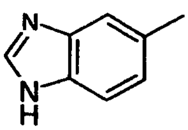
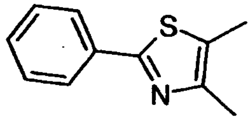
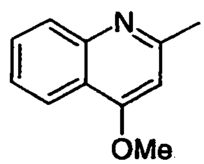
wherein R^{15} is:

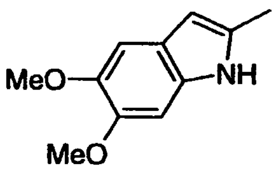
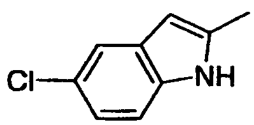
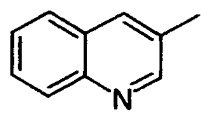


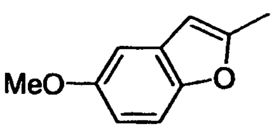
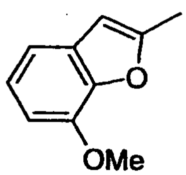
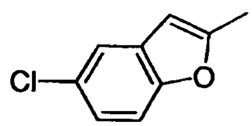
 ;  ;  ;

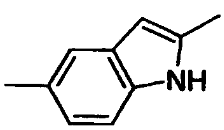
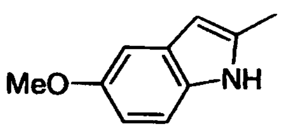
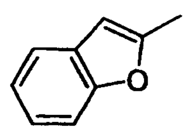
 ;  ;  ;

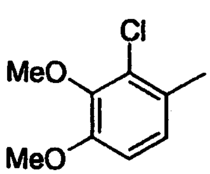
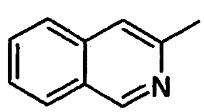
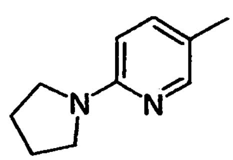
 ;  ;  ;

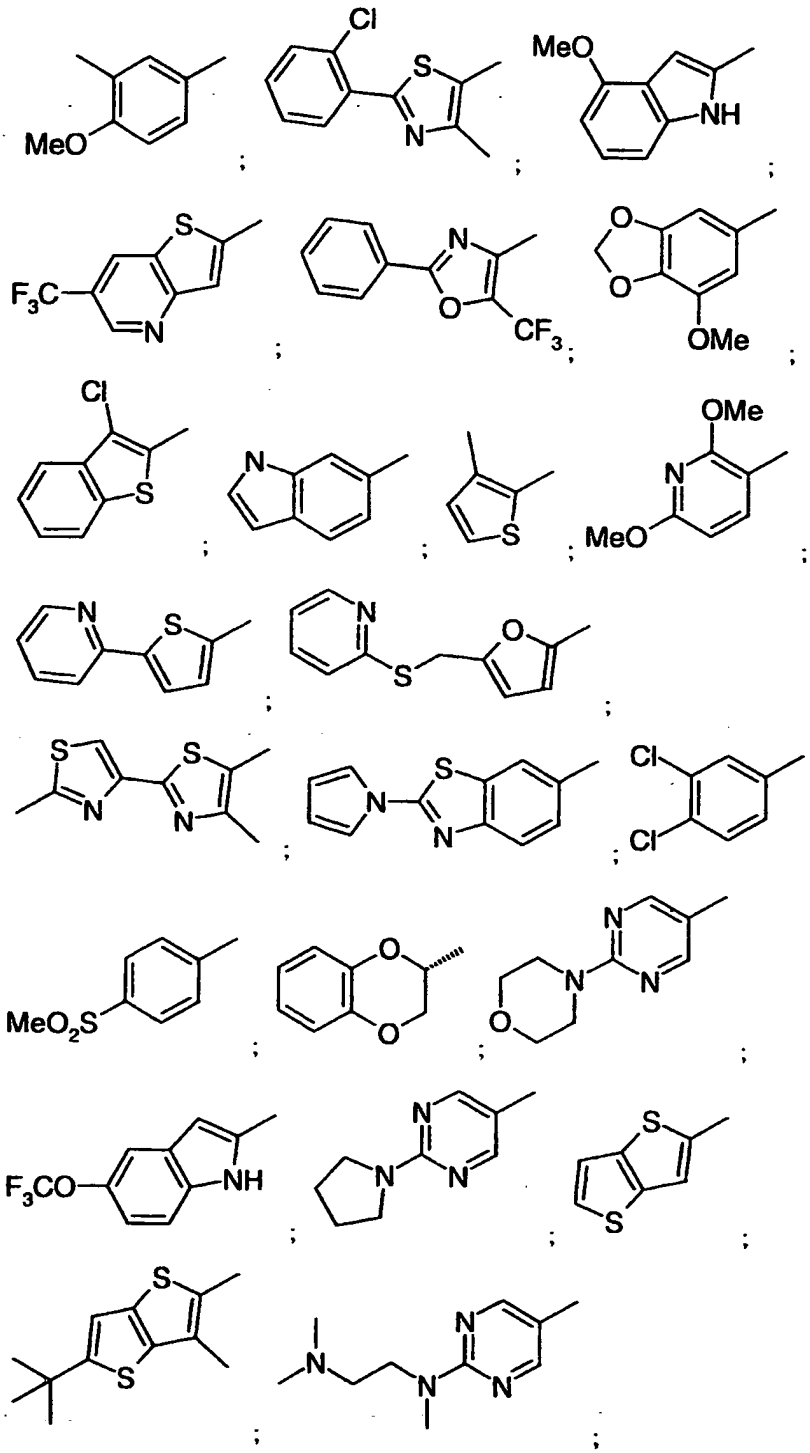
 ;  ;  ;

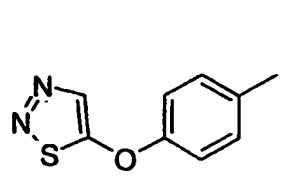
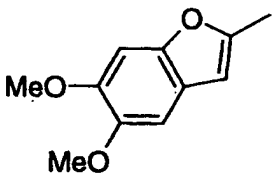
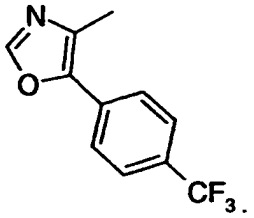
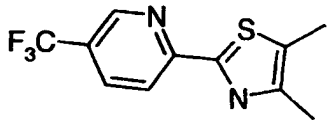
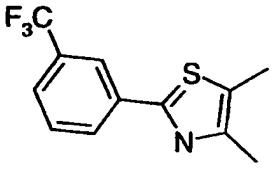
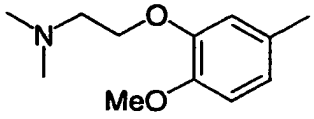
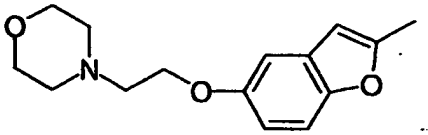
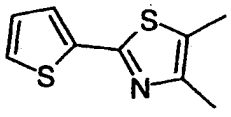
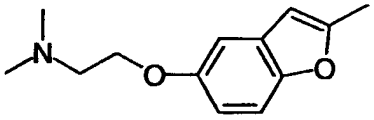
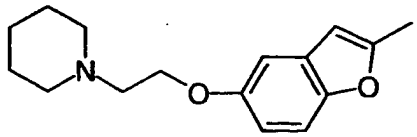
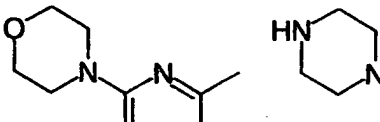
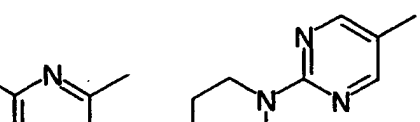
 ;  ;  ;

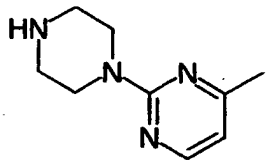
 ;  ;  ;

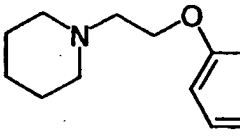
 ;  ;  ;

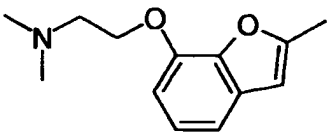
 ;  ;  ;




;

;

;

;

;

;

;

;

;

;

;

;

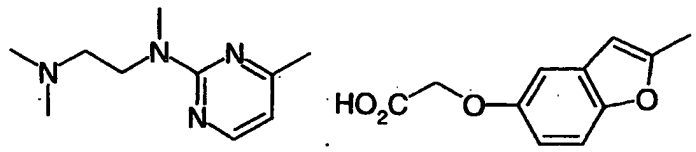
;

;

;

;

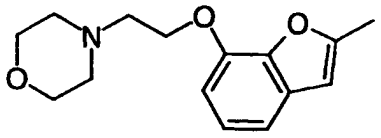
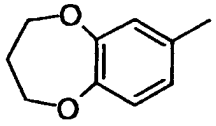
;

;

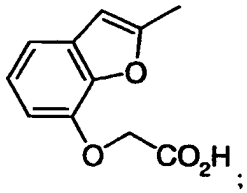
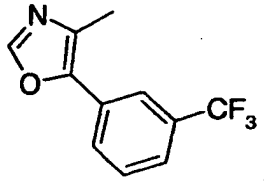
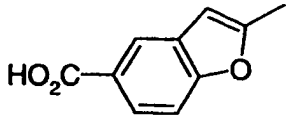
;

;


;

;


;

;

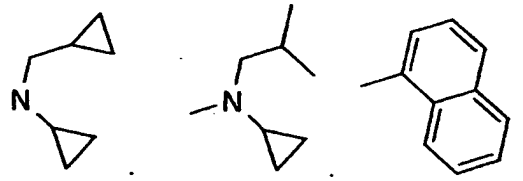

;

;


;and

R16 is selected from the group consisting of:

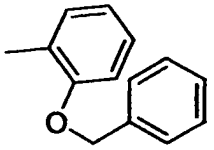
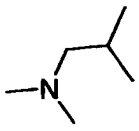
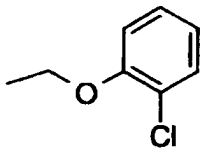

; and

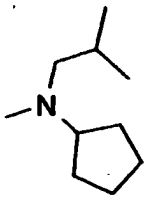
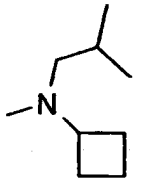
L is preferably:


;

;

;


;

;

;


;

;

Compounds of Formula I selected from the following group are particularly preferred embodiments of the present invention:

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-leucinyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(2 -pyridinylmethoxycarbonyl)-L-β -*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-methylpicolinoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[N-(3,4-difluorobenzoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-(3-propyloxypicolinoyl)-L-leucinyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrazolyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[N-[6-(1-imidazolyl)nicotinoyl]-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-[N-methyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(4-trofluoromethylphenyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[N-(6-methylpicolinoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide;

N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-(6-phenyldicotinoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-β -*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(2-chlorophenoxymethyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-leucinyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide;

N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[N-(5-butylpicolinoyl)-L-β-cyclopropylalanyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-imidazolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrazolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-methylenedioxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylacetyl)-L-β-cyclopropylalanyl]hydrazide;

N-[N-(benzothiazol-6-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-(N-benzothiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-hydroxymethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-hydroxymethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-(N-benzothiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-indole-2-ylcarbonyl-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-propyloxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-(2-pyridinyl)benzoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethylbenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-(N-benzothiazol-6-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-benzothiophen-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyll-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-(N-benzothiophen-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenylimidazol-4-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4,5-trimethoxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-hydroxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-4-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-5-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-(N-benzimidazol-5-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methyl-2-phenylthiazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyquinolin-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[N-(5-chloroindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-benzothiazol-6-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-flurorbenzimidazol-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-quinolin-3-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(7-methoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[N-(5-chlorobenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethoxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-(N-benzofuran-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[N-(2-chloro-3,4-dimethoxybenzoyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-isoquinolin-3-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-2-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-(N-benzofuran-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolidinyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methyl-2-phenylthiazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(5-chlorobenzofuran-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-(N-benzimidazol-5-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(5-chloroindole-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxy-3-methylbenzoyl)-L-leucinyl]hydrazide;

N-[N-[2-(2-chlorophenyl)-4-methylthiazol-5-ylcarbonyl]-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-trifluoromethyl-4-azabenzothiophen-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-phenyl-5-trifluoromethyloxazol-4-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyquinolin-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methoxy-4,5-methylenedioxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-2-ylcarbonyl-L-leucinyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(7-methoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(3-chlorobenzothiophen-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-6-ylcarbonyl-L-leucinyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methylthiophene-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,6-dimethoxynicotinoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-pyridinyl)thiophen-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-mercaptopyridinylmethyl)furan-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-6-ylcarbonyl-L-leucinyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-methylthiazol-4-yl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolyl)benzothiazol-6-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dichlorobenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methanesolfonylbenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-phenyl-5-trifluoromethyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[N-[2-(2-chlorophenyl)-4-methylthiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclohexylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-trifluoromethyl-4-azabenzothiophen-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,6-dimethoxynicotinoyl)-L-leucinyl]hydrazide;

(2S)-N-(N-benzodioxan-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-pyridinyl)thiophen-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-propionyl-L-leucinyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(4-morpholino)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-methylthiazol-4-yl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolyl)benzothiazol-6-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-trifluoromethoxyindol-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolidino)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-(N-butyryl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methylbutyryl)-L-leucinyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-cyclohexylglycinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-thieno[2,3-b]thiophen-2-ylcarbonyl-L-leucinyl)hydrazide;

N-[N-(5-*tert*-butyl-3-methylthieno[2,3-b]thiophen-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(1,2,3-thiadiazol-5-yloxy)benzoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-(4-triflouormethylphenyl)oxazol-4-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(3-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-thienyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(1-piperidinyl)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-thieno[2,3-b]thiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(4-morpholino)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-piperazinyl)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(1-piperidinyl)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]- N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[N-(5-carboxymethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3,4-(1,3-propylenedioxy)benzoyl]-L-leucinyl]hydrazide;

N-[N-(7-carboxymethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-(3-triflouormethylphenyl)oxazol-4-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[N-(5-carboxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide; and

N-[N-(7-carboxymethoxybenzofuran-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide.

Definitions

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to Formula I *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

The term "amino acid" as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

"C_{1-6}alkyl" as applied herein is meant to include substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C_{1-6}alkyl group may be optionally substituted independently by one to five halogens, S R^{16}, O R^{16}, $N(R^{16})_2$, $C(O)N(R^{16})_2$, carbamyl or C_{1-4}alkyl, where R^{16} is C_{1-6}alkyl. C_0alkyl means that no alkyl group is present in the moiety. Thus, Ar-C_0alkyl is equivalent to Ar.

"C_{3-11}cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane.

"C_{2-6} alkenyl" as applied herein means an alkyl group of 2 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C_{2-6}alkenyl includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included.

"C_{2-6}alkynyl" means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C_{2-6} alkynyl includes acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne.

"Halogen" means F, Cl, Br, and I.

As used herein "Ar" represents phenyl or naphthyl, optionally substituted by one or more of Ph-C_{0-6}alkyl, Het-C_{0-6} alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, Ph-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, NR^8R^9, Het-S-C_{0-6}alkyl, $(CH_2)_{1-6}OH$, $(CH_2)_{1-6}NR^8R^9$, $O(CH_2)_{1-6}NR^8R^9$, $(CH_2)_{0-6}CO_2R'$, $O(CH_2)_{1-6}CO_2R'$, $(CH_2)_{1-6}SO_2$, CF_3, OCF_3 or halogen; Ph and Het may be optionally substituted with one or more of C_{1-6}alkyl, C_{1-6}alkoxy, OH, $(CH_2)_{1-6}NR^8R^9$, $O(CH_2)_{1-6}NR^8R^9$, CO_2R', CF_3, or halogen; two C_{1-6}alkyl or C_{1-}

$_{6}$alkoxy groups may be combined to form a 5-7 membered ring, saturated or unsaturated, fused onto the Ar ring;

As used herein "Ar' "represents phenyl or naphthyl, optionally substituted by one or more of Ph-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, Ph-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}NR^8R^9$, $O(CH_2)_{1-6}NR^8R^9$, or halogen; Ph may be optionally substituted with one or more of C_{1-6}alkyl, C_{1-6}alkoxy, OH, $(CH_2)_{1-6}NR^8R^9$, $O(CH_2)_{1-6}NR^8R^9$, CO_2R', or halogen; two C_{1-6}alkyl groups may be combined to form a 5-7 membered ring, saturated or unsaturated, fused onto the Ar' ring;

As used herein "Het" or "heterocyclic" represents a stable 5- to 7-membered monocyclic, a stable 7- to 10-membered bicyclic, or a stable 11- to 18-membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may be optionally substituted as with Ar (including on the nitrogens) Examples of such heterocycles include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Het can be optionally substituted as with Ar (including on the nitrogens).

"5-7 membered ring, saturated or unsaturated, fused onto the Ar ring" means a fused bicyclic ring system such as indane, 1,2,3,4-tetrahydrodecalin, methylenedioxyphenyl, 1,2-ethylenedioxyphenyl and 1,3-propylenedioxyphenyl.

Here and throughout this application the term C_0 denotes the absence of the substituent group immediately following; for instance, in the moiety ArC_{0-6}alkyl, when C is 0, the substituent is Ar, e.g., phenyl. Conversely, when the moiety ArC_{0-6}alkyl is identified as a specific aromatic group, e.g., phenyl, it is understood that C is 0.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the

fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical.

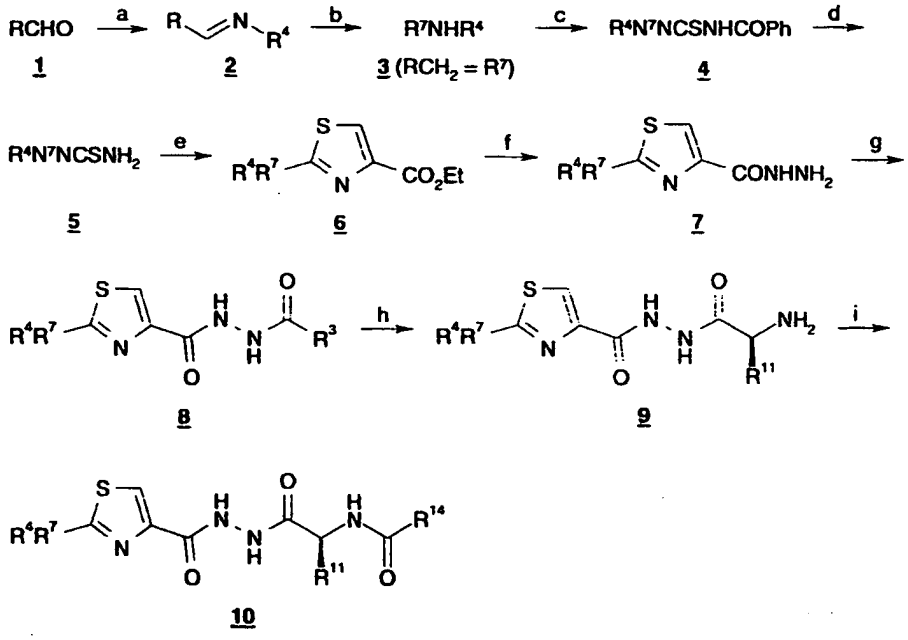
Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP is 2,6-dimethylaminopyridine, EDC refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide. HOBT refers to 1-hydroxybenzotriazole, DMF refers to dimethyl formamide, BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, DMAP is dimethylaminopyridine, NMM is N-methylmorpholine, TFA refers to trifluoroacetic acid, THF refers to tetrahydrofuran. Jones reagent is a solution of chromium trioxide, water, and sulfuric acid well-known in the art.

Methods of Preparation

The compounds of the present invention may be conveniently prepared by the methods set forth in Schemes 1 - 3 below.

Compounds of the formula I wherin X = S, Y = CH, Z = N and L = NR^4R^7, are prepared by methods analogous to those described in Scheme 1.

Scheme 1



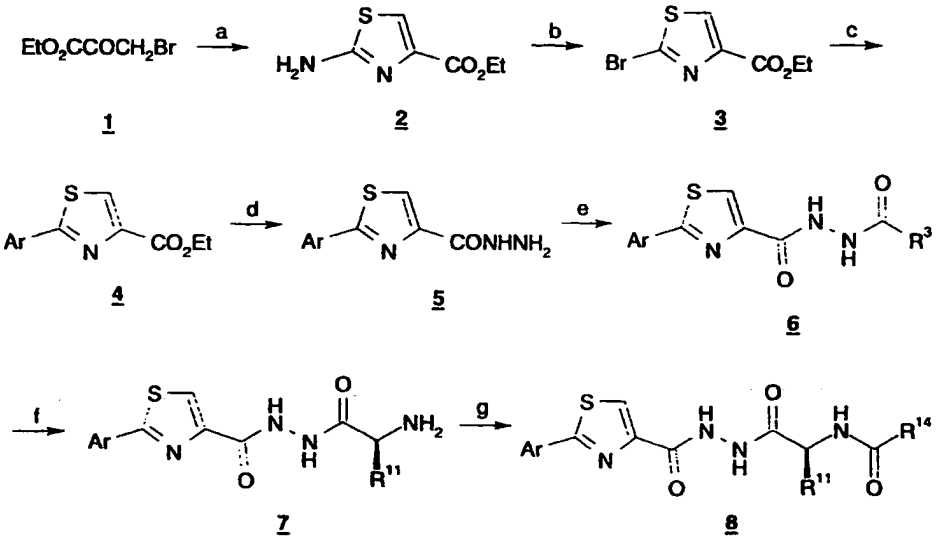
a) R^4NH_2, CH_2Cl_2; b) $Na(OAc)_3BH$, CH_2Cl_2; c) $PhCONCS$, $CHCl_3$; d) K_2CO_3, MeOH, H_2O; e) EtO_2CCOCH_2Br, EtOH; f) $H_2NNH_2 \cdot H_2O$, EtOH; g) R^3CO_2H, EDC·HCl, 1-HOBT, DMF; h) TFA, CH_2Cl_2; i) $R^{14}CO_2H$, EDC·HCl, 1-HOBT, DMF.

An aldehyde (such as cyclopropanecarboxaldehyde or isobutyraldehyde) (1-Scheme 1) was treated with a primary amine (such as cyclopropylamine, cyclobutylamine or cyclopentylamine) in methylene chloride to provide 2-Scheme 1, which was treated with sodium triacetoxyborohydride in methylene chloride to afford 3-Scheme 1. Treatment of 3-Scheme 1 with benzoyl isothiocyanate in chloroform provided 4-Scheme 1, which was treated with potassium carbonate in methanol/water to give 5-Scheme 1. Treatment of 5-Scheme 1 with ethyl bromopyrivate in ethanol provided 6-Scheme 1, which was treated with hydrazine hydrate in ethanol to give 7-Scheme 1. Treatment of 7-Scheme 1 with a carboxylic acid (such as N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, N-tert-butoxycarbonyl-L-leucine, N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucine, N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, N-(2-pyridinylmethoxycarbonyl)-L-leucine, (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane, N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanine, N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine, N-*tert*-butoxycarbonyl-L-β-cyclohexylalanine or N-*tert*-butoxycarbonyl-L-cyclohexylglycine) and a peptide coupling reagent (such as EDC·HCl/1-HOBT) in an aprotic solvent (such as DMF) provided 8-Scheme 1. When R^3CO_2H was a N-*tert*-butoxycarbonyl protected amino acid, treatment of 8-Scheme 1 with trifluoroacetic acid in dichloromethane provided 9-Scheme 1, which was treated with a carboxylic acid (such as 6-phenylnicotinic acid, 4-(2-pyridinyl)benzoic acid, 6-methylpicolinic acid, 3,4-difluorobenzoic acid, 4-methylimidazole-5-carboxylic acid, 5-butylpicolinic acid, 6-(1-pyrrolyl)nicotinic acid, 3,4-dimethoxybenzoic acid, 6-(1-imidazolyl)nicotinic acid, 6-(1-pyrazolyl)nicotinic acid, 3,4-methylenedioxybenzoic acid, 4-methoxybenzoic acid, 5-methyl-2-phenyl-4-oxazoleacetic acid, benzothiazole-6-carboxylic acid, 4-trifluoromethylbenzoic acid, benzothiophene-2-carboxylic acid, 4-methyl-2-(4-trifluoromethylphenyl)thiazole-5-carboxylic acid, 4-hydroxymethylbenzoic acid, 2,3-dihydrobenzofuran-5-carboxylic acid, indole-2-carboxylic acid, 1-methylindole-2-carboxylic acid, 4-trifluoromethoxybenzoic acid, 4-propyloxybenzoic acid, 3-(2-pyridinyl)benzoic acid, 5-methyl-2-phenyloxazole-4-carboxylic acid, 5-fluoroindole-2-carboxylic acid, 4(5)-methyl-2-phenylimidazole-5(4)-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 5-hydroxyindole-2-carboxylic acid, indole-4-carboxylic acid, indole-5-carboxylic acid, benzimidazole-5-carboxylic acid, 4-methyl-2-phenylthiazole-5-carboxylic acid, 4-methoxyquinoline-2-carboxylic acid, 5,6-dimethoxyindole-2-carboxylic acid, 5-chloroindole-2-carboxylic acid, 4-fluorobenzimidazole-2-carobxylic acid,

quinoline-3-carboxylic acid, 5-methoxybenzofuran-2-carobxylic acid, 5-methoxybenzofuran-2-carobxylic acid, 5-chlorobenzofuran-2-carobxylic acid, 5-methylindole-2-carboxylic acid, 5-methoxyindole-2-carboxylic acid, benzofuran-2-carboxylic acid, 2-chloro-3,4,-dimethoxybenzoic acid, isoquinoline-2-carboxylic acid, 6-(1-pyrrolidino)nicotinic acid, 4-methoxy-3-methylbenzoic acid, 2-(2-chlorophenyl)-4-methylthiazole-5-carboxylic acid, 4-methoxyindole-2-carboxylic acid, 6-trifluoromethyl-4-azabenzothiophene-2-carboxylic acid, 2-phenyl-5-trifluoromethyloxazole-4-carboxylic acid, 3-methoxy-4,5-methylenedioxybenzoic acid, 3-chlorobenzothiophene-2-carboxylic acid, indole-6-carobxylic acid, 3-methylthiophene-2-carboxylic acid, 2,6-dimethxoynicotinic acid, 2-(2-pyridinyl)thiophene-5-carboxylic acid, isovaleric acid, 2-(2-mercaptopyridinylmethyl)furan-5-carboxylic acid, 4-methyl-2-(2-methylthiazol-4-yl)thiazole-5-carboxylic acid, 2-(1-pyrrolyl)benzothiazole-6-carboxylic acid, 3,4-dichlorobenzoic acid, 4-methanesulfonylbenzoic acid, benzodioxane-2-carboxylic acid, propionic acid, 2-(4-morpholino)pyrimidine-5-cargboxylic acid, 5-trifluoromethxoyindole-2-carboxylic acid, 2-(1-pyrrolidino)pyrimidine-5-carboxylic acid, butyric acid, thieno[2,3-b]thiophene-2-carboxylic acid, 5-*tert*-butyl-3-methylthieno[2,3-b]thiophene-2-carboxylic acid, 2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylic acid, 4-(1,2,3-thiadiazol-5-yloxy)benzoic acid, 5,6-dimethoxybenzofuran-2-carboxylic acid, 5-(4-triflouormethylphenyl)oxazole-4-carboxylic acid, 4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazole-5-carboxylic acid, 4-methyl-2-(3-trifluoromethylphenyl)thiazole-5-carboxylic acid, 3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoic acid, 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid, 4-methyl-2-(2-thienyl)thiazole-5-carboxylic acid, 5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid, 5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid, 2-(4-morpholino)pyrimidine-4-carboxylic acid, 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylic acid, 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylic acid, 7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid, 7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid, 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-4-carboxdylic acid, 5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid, 7-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid, 3,4-(1,3-propylenedioxy)benzoic acid, 7-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid, 5-(3-triflouormethylphenyl)oxazole-4-carboxylic acid or 5-*tert*-butoxycarbonylbenzofuran-2-carboxylic acid) and a peptide coupling reagent (such as EDC·HCl/1-HOBT) in an aprotic solvent (such as DMF) to give 10-Sheme 1. When $R^{14}CO_2H$ is 2-(4-*tert*-

butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylic acid, 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylic acid, 5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid, 7-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid or 5-*tert*-butoxycarbonylbenzofuran-2-carboxylic acid, the tert-butyl protecting groups were removed from 10-Scheme 1 by treatment with trifluoroacetic acid in dichloromethane.

Scheme 2



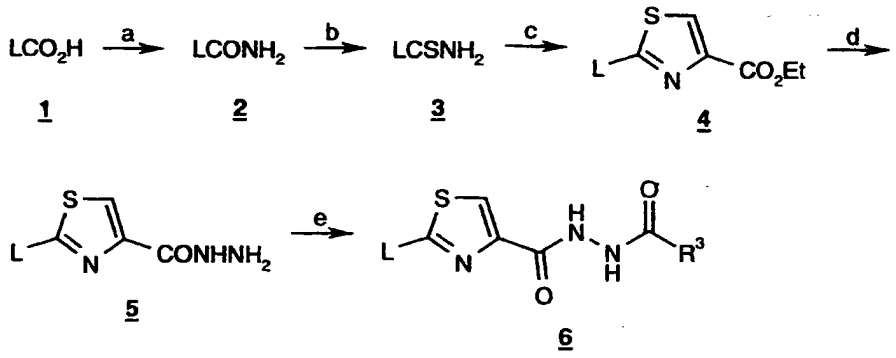
a) Thiourea, EtOH; b) i. $NaNO_2$, 16% aqueous HBr; ii. CuBr, 16% aqueous HBr; iii. HBr (cat.), EtOH; c) $ArB(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, toluene, EtOH, H_20; d) $H_2NNH_2 \cdot H_2O$, EtOH; e) R^3CO_2H. EDC·HCl, 1-HOBT, DMF; f) TFA, CH_2Cl_2; g) $R^{14}CO_2H$, EDC·HCl, 1-HOBT, DMF.

Compounds of the formula I wherin X = S, Y = CH, Z = N and L = Ar, are prepared by methods analogous to those described in Scheme 2. Ethyl bromopyruvate (1-Schem 2) was treated with thiourea in refluxing ethanol to provide 2-Scheme 2, which wass treated successively with sodium nitrite and copper (I) bromide in 16% aqueous HBr, and the product was heated in ethanol with a catalytic amount of HBr to give 3-Scheme 2. Treatment of 3-Scheme 2 with an arylboronic acid (such as 1-naphthylboronic acid or 2-benzyloxyphenylboronic acid), tetrakis(triphenylphosphine)pallladium(0) and sodium bicarbonate in refluxing toluene/ethaonl/water provided 4-Scheme 2, which was treated with with hydrazine hydrate in ethanol to provide 5-Scheme 2. Treatment of 5-Scheme 2 with a carboxylic acid (such as N-*tert*-butoxycarbonyl-L-leucine, (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane, N-(5-butyl-2-

pyridinylmethoxycarbonyl)-L-leucine or 2-(1-naphthyl)thiazole-4-carboxylic acid) and a peptide coupling reagent (such as EDC·HCl/1-HOBT) in an aprotic solvent (such as DMF) provided 6-Scheme 2. When R^3CO_2H was N-*tert*-butoxycarbonyl-L-leucine, treatment of 6-Scheme 2 with trifluoroacetic acid in dichloromethane provided 7-Scheme 2, which was treated with a carboxylic acid (such as 3,4-dimethoxybenzoic acid, 3,4-difluorobenzoic acid, 5-butylpicolinic acid, 3-propyloxypicolinic acid, 6-(1-pyrrolyl)nicotinic acid, 6-(1-pyrazolyl)nicotinic acid, 6-(1-imidazolyl)nicotinic acid, 6-(4-trofluoromethylphenoxy)nicotinic acid, 6-methylpicolinic acid, 4-(2-pyridinyl)benzoic acid or 6-phenylnicotinic acid) and a peptide coupling reagent (such as EDC·HCl/1-HOBT) in an aprotic solvent (such as DMF) to give 8-Sheme 2.

Compounds of the formula I wherin X = S, Y = CH and Z = N, are prepared by methods analogous to those described in Scheme 1.

Scheme 3



a) *i*-BuOCOCl, NMM, NH_3, THF; b) Lawesson's reagent, THF; c) i. EtO_2CCOCH_2Br, CH_2Cl_2; ii. TFAA, Py, CH_2Cl_2; d) $H_2NNH_2·H_2O$, EtOH; e) R^3CO_2H, EDC·HCl, 1-HOBT, DMF.

Treatment of 1-Scheme 3 with isobutyl chloroformate, N-methylmorpholine and ammonia in THF provided 2-Scheme 3, which was treated with Lawesson's reagent in THF to give 3-Scheme 3. Treatment of 3-Scheme 3 with ethyl bromopyruvate in dichloromethane followed by treatment with trifluoroacetic anhydride and pyridine in methylene chloride provided 4-Scheme 3, which was treated with hydrazine hydrate in ethanol to give 5-Scheme 3. Treatment of 5-Scheme 3 with a carboxylic acid (such as (1S)-1-benzyloxycarbonylamino-1-(4-carboxythiazol-2-yl)-3-methylbutane) and a peptide

coupling reagent (such as EDC·HCl/1-HOBT) in an aprotic solvent (such as DMF) gave 6-Scheme 3.

Referring to the methods of preparing the compounds of Formula I set forth in Schemes 1-3 above, the skilled artisan will appreciate that the present invention includes all novel intermediates required to make the compounds of Formula I. More specifically, the present invention includes the following compounds:

3-(6-methyl)pyridylcarbinol;

L-β-*tert*-butylalanine methyl ester;

β-isocyanato-L-β-*tert*-butylalanine methyl ester;

N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

N-cyclopropylmethylcyclopropylamine;

N-benzoyl-N'-cyclopropyl-N'-cyclopropylmethylthiourea;

N-cyclopropyl-N-cyclopropylmethylthiourea;

ethyl 2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazole-4-carboxylate;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

ethyl 6-phenylnicotinate;

6-phenylnicotinic acid;

N-cyclopropyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclopropyl-N'-(2-methylpropyl)thiourea;

N-cyclopropyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

4-carbomethoxyphenylboronic acid;

methyl 4-(2-pyridinyl)benzoate;

4-(2-pyridinyl)benzoic acid;

ethyl 2-(1-naphthyl)thiazole-4-carboxylate;

2-(1-naphthyl)thiazole-4-ylcarbonylhydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanine;

N-(N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-*tert*-butylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

2-(2-chlorophenoxymethyl)thiazol-4-ylcarbonylhydrazide;

N-cyclopentyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclopentyl-N'-(2-methylpropyl)thiourea;

N-cyclopentyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

(S)-2-*tert*-butoxycarbonylaminopent-4-enoic acid;

N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine methyl ester;

N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-cyclopropylalanyl)-N'-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-cyclopropylalanyl)hydrazide;

N-cyclobutyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclobutyl-N'-(2-methylpropyl)thiourea;

N-cyclobutyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

L-β-cyclopropylalanine methyl ester;

β-isocyanato-L-β-cyclopropylalanine methyl ester;

N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanine methyl ester;

N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanine;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-cyclopropylalanyl)hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclohexylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-cyclohexylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 2-(4-morpholino)pyrimidine-5-carboxylate;

2-(4-morpholino)pyrimidine-5-carboxylic acid;

ethyl 2-(1-pyrrolidino)pyrimidine-5-carboxylate;

2-(1-pyrrolidino)pyrimidine-5-carboxylic acid;

N-(N-*tert*-butoxycarbonyl-L-β-cyclohexylglycinyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-(L-β- cyclohexylglycinyl)-N'-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]hydrazide;

ethyl 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylate;

2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylic acid;

ethyl 5-hydroxybenzofuran-2-carboxylate;

ethyl 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylate;

5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid;

ethyl 5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylate;

5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid;

ethyl 5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylate;

5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid;

ethyl 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylate;

2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylic acid;

N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylate;

2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylic acid;

N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 7-hydroxybenzofuran-2-carboxylate;

ethyl 7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylate;

7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid;

ethyl 7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylate;

7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid;

ethyl 7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylate;

7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid;

ethyl 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-4-carboxylate;

2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-4-carboxylic acid;

2-(1-naphthyl)thiazole-4-carboxylic acid;

benzyl 5-hydroxybenzofuran-2-carboxylate;

benzyl 5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylate;

5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid;

N-[N-(5-*tert*-butoxycarbonylmethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 7-[2-(1-morpholino)ethoxy]benzofuran-2-carboxylate;

7-[2-(1-morpholino)ethoxy]benzofuran-2-carboxylic acid;

benzyl 7-hydroxybenzofuran-2-carboxylate;

benzyl 7-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylate;

7-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid;

N-[N-(7-*tert*-butoxycarbonylmethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

benzyl 5-methoxycarbonylbenzofuran-2-carboxylate;

5-methoxycarbonylbenzofuran-2-carboxylic acid;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxycarbonylbenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide; and

N-[N-(7-*tert*-butoxycarbonylmethoxybenzofuran-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

and all salts, hydrates and solvates thereof.

The starting materials used herein are commercially available amino acids or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

Coupling methods to form amide bonds herein are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984. are generally illustrative of the technique and are incorporated herein by reference.

Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York (1981). The term "amino protecting groups" generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

Acid addition salts of the compounds of Formula I are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts. Halides, sulfate, phosphate, alkanoates (such as acetate and trifluoroacetate), benzoates, and sulfonates (such as mesylate) are examples of anions present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of Formula I may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of Formula I prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and

compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

Utility of the Present Invention

The compounds of Formula I are useful as protease inhibitors, particularly as inhibitors of cysteine and serine proteases, more particularly as inhibitors of cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly as inhibitors of cysteine proteases of the cathepsin family, most particularly as inhibitors of cathepsin K. The present invention also provides useful compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present compounds are useful for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy; and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease; hypercalcemia of malignancy, and metabolic bone disease.

Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

The present invention also provides methods of treatment of diseases caused by pathological levels of proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof a compound of the present invention. The present invention especially provides methods of treatment of diseases caused by pathological levels of cathepsin K, which methods comprise administering to an animal, particularly a

mammal, most particularly a human in need thereof an inhibitor of cathepsin K, including a compound of the present invention. The present invention particularly provides methods for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration to a patient of an effective amount of a compound of Formula I, alone or in combination with other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss or to increase bone mass.

For acute therapy, parenteral administration of a compound of Formula I is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

Biological Assays

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Determination of cathepsin K proteolytic catalytic activity

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemitsry,* 1989, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\ app}) + A] \qquad (1)$$

where v is the velocity of the reaction with maximal velocity V_m, A is the concentration of substrate with Michaelis constant of K_a, and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[AMC] = v_{ss}\, t + (v_0 - v_{ss})\,[1 - exp\,(-k_{obs}t)]\,/\,k_{obs} \qquad (2)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs} / [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 1988, *61*, 201).

Human Osteoclast Resorption Assay

Aliquots of osteoclastoma-derived cell suspensions were removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 min on ice The cell suspension was mixed frequently.

The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear cells were enumerated in an improved Neubauer counting chamber.

Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes away the toxic azide preservative). The medium was removed by immobilizing the beads on a magnet and is replaced with fresh medium.

The beads were mixed with the cells and the suspension was incubated for 30 min on ice. The suspension was mixed frequently. The bead-coated cells were immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to $1.5x10^4$/mL in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension (per treatment) were decanted into 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 uM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/mL) and an isotype control (IgG2a diluted to 100 ug/mL). The tubes were incubate at 37°C for 30 min.

0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 h. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 h. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 min., following which they were washed in water and incubated in buffer for 5 min at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 min at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

The TRAP positive osteoclasts were enumerated by bright-field microscopy and were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

General

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (d) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers

(cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

Examples

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

Example 1

Preparation of N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide

a) 3-(6-methyl)pyridylcarbinol

To a stirring solution of ethyl 6-methylnicotinate (1.3 g, 8.6 mmol) in diethyl ether (50 mL) at 0 βC was added dropwise lithium aluminum hydride (9.5 mL, 9.5 mmol, 1.0M in THF). After stirring at room temperature for 2h, the reaction was quenched by successive addition of water (0.360 mL), 15% NaOH (0.360 mL), and water (1.1 mL). The mixture was filtered and the filtrate concentrated to yield the title compound as a yellow oil (0.852 g, 81%). MS (ESI): 124.0 $(M+H)^+$.

b) L-β-*tert*-butylalanine methyl ester hydrochloride

To a suspension of L-β-*tert*-butylalanine (2.0 g, 13.8 mmol) in 2,2-dimethoxypropane (75 mL) was added concentrated HCl (12 mL). After standing at room temperature for 16h, the mixture was concentrated and the residue dissolved in ethyl acetate. The organic layer was washed with 7.5% aqueous sodium carbonate (2x) then dried ($MgSO_4$), filtered and concentrated to yield the free base which was treated with 1.0 eq HCl in diethyl ether. The precipitate was filtered off to yield the hydrochloride salt as a white solid (1.32 g, 49%). MS (ESI): 159.7 $(M+H)^+$.

c) β-isocyanato-L-β-tert-butylalanine methyl ester

To a suspension of the compound of Example 1(b) (1.32 g, 6.75 mmol) in dichloromethane (50 mL) was added pyridine (2.1 g, 27 mmol). The solution was taken to

0 βC and a solution of triphosgene (0.862 g, 2.90 mmol) in dichloromethane (10 mL) was added dropwise over 40 min. After stirring at 0 βC for 2h, the solution was partitioned between 0.5N HCl and dichloromethane. The organic layer was washed successively with cold 0.5N HCl, cold water, and cold brine, dried ($MgSO_4$), filtered and concentrated to yield the title compound as a pale yellow oil (1.24 g, 99%). ^{1}HNMR (400 MHz, $CDCl_3$) β 3.99 (dd, 1H), 3.81 (s, 3H), 1.89 (dd, 1H), 1.58 (dd, 1H), 0.97 (s, 9H).

d) N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester

A solution of the compound of Example 1(c) (0.404 g, 2.18 mmol) and the compound of Example 1(a) (0.269 g, 2.18 mmol) in toluene (3 mL) was heated at reflux for 16h. The solution was then concentrated and purified by column chromatography (silica gel; ethyl acetate/hexane) to yield the title compound as a yellow solid (0.447 g, 71%). MS (ESI): 309.3 $(M+H)^+$.

e) N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine

To a stirring solution of the compound of Example 1(d) (0.447 g, 1.45 mmol) in THF (7.0 mL) and water (7.0 mL) was added lithium hydroxide monohydrate (0.069 g, 1.60 mmol). After stirring at reflux for 16h, the solution was concentrated and the residue was dissolved in water and acidified with 1eq 1N HCl. The mixture was frozen and placed on a lyophilizer for 16h to yield the title compound as an off-white solid (0.426 g, 100%). MS (ESI): 295.2 $(M+H)^+$.

f) N-cyclopropylmethylcyclopropylamine

Cyclopropylamine (6.6 g, 115.4 mmol, 8.0 mL) and cyclopropylcarboxaldehyde (8.09 g, 115.4 mmol, 8.6 mL) were dissolved in methylene chloride (40 mL) and allowed to stir at room temperature. After two hours, the mixture was dried ($MgSO_4$), filtered and concentrated to afford the pure imine, which was dissolved in ether (50 mL), the solution was cooled to 0 °C and lithium aluminum hydride (170 mmol, 170 mL, 1 M in ether) was added slowly. The solution mixture was stirred for two hours and then quenched at 0 °C with water, sodium hydroxyde (15%), water. The solid was removed by filtration and washed with ether. The filtrate was dried ($MgSO_4$), filtered and concentrated to afford the title compound as a colorless liquid (6.10 g, 47%). MS (ESI): 111.9 $(M+H)^+$.

g) N-benzoyl-N'-cyclopropyl-N'-cyclopropylmethylthiourea

The compound of Example 1(f) (6.10 g, 54.86 mmol) was dissolved in chloroform (100 mL) and benzoyl isothiocyanate (8.95 g, 54.86 mmol, 8.00 mL) was added. After stirring 45 minutes at room temperature, the solution was concentrated to give the title compound as an orange solid (15.05 g, 100%). MS (ESI): 275.1 $(M+H)^+$.

h) N-cyclopropyl-N-cyclopropylmethylthiourea

The compound of Example 1(g) (15.05 g, 54.86 mmol) was dissolved in methanol (100 mL) and water (100 mL), potassium carbonate (22.7 g, 164.6 mmol) was added and the solution was heated at reflux overnight. The reaction mixture was concentrated, redissolved in ethyl acetate, washed with sodium bicarbonate, water and dried ($MgSO_4$), filtered and concentrated to afford the title compound as a yellow solid (9.34 g, 100%). MS (ESI): 170.9 (M).

i) ethyl 2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazole-4-carboxylate

The compound of Example 1(h) (9.34 g, 54.86 mmol) was dissolved in 50 mL of ethanol upon heating. The solution was cooled to room temperature and ethylbromopyruvate (10.7 g, 54.86 mmol, 6.8 mL) was added. The reaction mixture was heated at reflux for 30 minutes, then concentrated. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with saturated brine, dried ($MgSO_4$), filtered and concentrated to give an orange oil. The crude product was passed trough silica gel eluting with ethyl acetate/ hexane (1:3) to give the title compound as a yellow oil (13.53 g, 93%). MS (ESI): 267.2 $(M+H)^+$.

j) N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide

The compound of Example 1(i) (13.53 g, 50.80 mmol) was dissolved in 100 mL ethanol and hydrazine monohydrate (25.4 g, 508 mmol, 24.6 mL) was added. The solution was heated at reflux for 2 hours, then concentrated. The crude product was passed trough silica gel eluting with 10% methanol in methylene chloride to give the title compound as a yellow solid (11.04 g, 86%). MS (ESI): 253.1 $(M+H)^+$.

k) N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide

To a stirring solution of the compound of Example 1(e) (160 mg, 0.48 mmol) in 2.5 mL of DMF was added the compound of Example 1(j) (120 mg, 0.48 mmol), 1-hydroxybenzotriazole (6.0 mg, 0.05 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (91 mg, 0.48 mmol). After stirring at room temperature for 16 h, the solution was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography on silica gel (6% methanol in methylene chloride) to afford the title compound as a white solid (200 mg, 80%). MS (ESI): 529.3 $(M+H)^+$.

Example 2

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-leucinyl]hydrazide

a) tetrakis[tris(o-tolyl)phosphine]palladium(0)

Palladium acetate (450 mg, 2.0 mmol) was dissolved in toluene (50 mL) and treated with tris(o-tolyl)phosphine (800 mg, 2.63 mmol). The solution was heated to 50°C for three minutes and cooled to room temperature. The solution was reduced to a quarter of its volume and, after addition of hexane (50 mL), the precipitate was filtered off and dried under vacuum to give the title compound as a yellow solid (670 mg, 71%), which was dissolved in dimethylacetamide (8.4 mL) and the catalyst solution was degassed and purged with argon several times before use.

b) ethyl 6-phenylnicotinate

Ethyl-6-chloronicotinate (1.7 g, 9.16 mmol), phenylboronic acid acid (1.675 g, 13.74 mmol) and potassium carbonate (2.5 g, 18.32 mmol) were dissolved in ortho-xylene (20 mL) and the solution was heated to 100°C. When the temperature was reached a freshly prepared solution of the compound of Example 2(a) (60 βL, 0.009 mmol) was injected and the reaction mixture was heated at 130°C overnight. Subsequently the cooled reaction mixture was extracted twice with methylene chloride. The combined organic layers were

washed with water. The solvent was then removed under vacuum to give a brown oil. The crude residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:10) to give the title compound as a white solid (2.035 g, 98%). MS (ESI): 228.2 $(M+H)^+$.

c) 6-phenylnicotinic acid

Following the procedure of Example 1(e), except substituting ethyl 6-phenylnicotinate for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as a white solid (165 mg, 10%). MS (ESI): 200.1 $(M+H)^+$.

d) N-cyclopropyl-N-(2-methylpropyl)amine

Cyclopropylamine (3.3 g, 57.7 mmol, 4.0 mL) and isobutyraldehyde (4.04 g, 57.7 mmol, 5.25 mL) were dissolved in methylene chloride (40 mL) and allowed to stir at room temperature. After two hours, the mixture was dried ($MgSO_4$), filtered and concentrated to afford the pure imine, which was dissolved in methylene chloride (200 mL), the solution was cooled to 0 °C and sodium triacetoxyborohydride (30.5 g, 144.25 mmol) was added. The mixture was allowed to stir for two hours and then washed with sodium bicarbonate (5% aqueous), dried ($MgSO_4$), filtered and concentrated to afford the title compound as a colorless liquid (2.25 g, 35%). MS (ESI): 114.1 $(M+H)^+$.

e) N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(g)-1(k), except substituting N-cyclopropyl-N-(2-methylpropyl)amine for N-cyclopropylmethylcyclopropylamine in step (g), and N-*tert*-butoxycarbonyl-L-leucine for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine in step (k), the title compound was prepared as a white solid (1.66 g, 96%). MS (ESI): 468.2 $(M+H)^+$.

f) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide

To a stirring solution of the compound of Example 2(e) (1.66 g, 3.54 mmol) in 10 ml of methylene chloride was added 5 mL of trifluoroacetic acid. After stirring one hour at room remperature the solution was concentrated and the residue was redissolved in methylene chloride, washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered and concentrated to afford the title compound as a yellow solid (1.30 g, 100%). MS (ESI): 368.3 $(M+H)^+$.

g) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-phenylnicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (200 mg, 69%). MS (ESI): 549.4 $(M+H)^+$.

Example 3

Preparation of N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(2 -pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(c)-1(k), except substituting 2-pyridylcarbinol for 6-methyl-3-pyridylcarbinol in step (d), the title compound was prepared as a white solid (123 mg, 70%). MS (ESI): 515.2 $(M+H)^+$.

Example 4

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide

a) 4-carbomethoxyphenylboronic acid

4-Formylbenzene boronic acid (2.05 g, 13.67 mmol) and potassium cyanide (6.2 g, 95.7 mmol) were dissolved in methanol (250 mL). Activated manganese dioxide (2.4 g, 273.4 mmol) was added and the mixture was stirred at room temperature for two days. The solution was then filtered through celite, concentrated and partitioned between ethyl acetate and hydrochloric acid (3N), then washed with water and saturated brine. The organic phase was dried ($MgSO_4$), filtered and concentrated to afford the title compound as a white solid (2.2 g, 89%). MS (ESI): 179.0 $(M-H)^+$.

b) methyl 4-(2-pyridinyl)benzoate

2-Bromopyridine (1.44 g, 9.12 mmol, 0.87 mL), the compound of Example 4(a) (2.135 g, 11.86 mmol) and tetrakis(triphenylphosphine)palladium(0) (210 mg, 0.18 mmol) were suspended in toluene (30 mL) and ethanol (30 mL) and sodium carbonate (2.5 g, 23.71 mmol) was then added. The mixture was stirred at 90°C overnight. The solution was partitioned between ethyl acetate and water, then washed successively with water and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated to give an orange solid. The crude residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:3 then 2:1 and 3:1) to give the title compound as a white solid (970 mg, 50%). MS (ESI): 214.1 $(M+H)^+$.

c) 4-(2-pyridinyl)benzoic acid

Following the procedure of Example 1(e), except substituting methyl 4-(2-pyridinyl)benzoate for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as a white solid (1.1 g, 100%). MS (ESI): 200.1 $(M+H)^+$.

d) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-(2-pyridinyl)benzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 44%). MS (ESI): 549.2 $(M+H)^+$.

Example 5

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-methylpicolinoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-methylpicolinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (130 mg, 86%). MS (ESI): 487.2 $(M+H)^+$.

Example 6

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3,4-difluorobenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (130 mg, 93%). MS (ESI): 508.2 $(M+H)^+$.

Example 7

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methylimidazole-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (80 mg, 69%). MS (ESI): 476.3 $(M+H)^+$.

Example 8

Preparation of N-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

a) ethyl 2-aminothiazole-4-carboxylate hydrobromide

Following the procedure of Example 1(i), except substituting thiourea for N-cyclopropyl-N-cyclopropylmethylthiourea, the title compound was prepared as as pale yellow crystals (132.74 g, 85%). MS (ESI): 172.9 $(M+H)^+$.

b) 2-bromothiazole-4-carboxylic acid

To a stirring suspension of the compound of Example 8(a) (32.11 g, 0.127 mol) in 16% HBr (aq) (40 0mL) at 0°C a solution of $NaNO_2$ (9.11 g, 0.132 mol) in water (16 mL) was added. After stirring for 35 min, CuBr (20.6 g, 0.144 mol) was added followed by an additional 150 mL of 16% HBr(aq). The mixture was heated at 70°C for 1h and immediately filtered. The filtrate was saturated with NaCl and extracted with ethyl acetate (2 x 500 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated to a brown solid. This was combined with solid collected by filtration and used without further purification or characterization in the next step.

c) ethyl 2-bromothiazole-4-carboxylate

The compound of Example 8(b) was heated at reflux in EtOH (1 L) for 1h then filtered. To the filtrate was added 48% (aq) HBr (3.2 mL). The solution was returned to reflux for 24h. After concentrating the solution, it was redissolved in EtOAc (1 L) and washed successively with saturated aqueous $NaHCO_3$ (1 L) and brine (1 L). The organic layer was dried ($MgSO_4$), filtered, decolorized with charcoal, filtered through Celite, and concentrated to give the title compound as a pale yellow solid (16.95 g, 56% from aminothiazole). ^{1}HNMR (400MHz, $CDCl_3$) β 8.13 (s, 1H), 4.41 (q, 2H), 1.40 (t, 3H).

d) ethyl 2-(1-naphthyl)thiazole-4-carboxylate

To a stirring mixture of the compound of Example 8(c) (13.7 g, 0.0581 mol), 1-naphthalene boronic acid (13.0 g, 0.0754 mol), and tetrakis(triphenylphosphine)palladium(0) (2.7 g, 4 mol%) in EtOH (125 mL) and toluene (125 mL) was added $NaHCO_3$ (151 mL, 1.0 M in water). After stirring at reflux for 4h the mixture was cooled and partitioned between 1N HCl (750 mL) and ethyl acetate (750 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/ hexane) to yield the title compound as a foamy solid. (10.4 g, 63%). MS (ESI): 284.2 $(M+H)^+$.

e) 2-(1-naphthyl)thiazole-4-ylcarbonylhydrazide

Following the procedure of Example 1(j), except substituting ethyl 2-(1-naphthyl)thiazole-4-carboxylate for ethyl 2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazole-4-carboxylate, the title compound was prepared as a pale yellow solid (9.7 g, 98%). MS (ESI): 270.1 $(M+H)^+$.

f) N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting 2-(1-naphthyl)thiazole-4-carbohydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and N-*tert*-butoxycarbonyl-L-leucine for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (10.38 g, 97%). MS (ESI): 483.3 $(M+H)^+$.

g) N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(f), except substituting N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide, the title compound was prepared as an off-white solid (8.02 g, 98%). MS (ESI): 383.2 $(M+H)^+$.

h) N-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3,4-dimethoxybenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.089 g, 50%). MS (ESI): 547.2 $(M+H)^+$.

Example 9

Preparation of N-[N-(3,4-difluorobenzoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3,4-difluorobenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.131 g, 77%). MS (ESI): 523.1 $(M+H)^+$.

Example 10

Preparation of N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-

cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-butylpicolinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.114 g, 64%). MS (ESI): 544.2 $(M+H)^+$.

Example 11

Preparation of N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-(3-propyloxypicolinoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3-propyloxypicolinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.060 g, 34%). MS (ESI): 546.2 $(M+H)^+$.

Example 12

Preparation of N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-(1-pyrrolyl)nicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.093 g, 52%). MS (ESI): 553.2 $(M+H)^+$.

Example 13

Preparation of N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrazolyl)nicotinoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-

cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-(1-pyrazolyl)nicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.130g, 72%). MS (ESI): 554.2 $(M+H)^+$.

Example 14

Preparation of N-[N-[6-(1-imidazolyl)nicotinoyl]-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-(1-imidazolyl)nicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.121 g, 67%). MS (ESI): 554.2 $(M+H)^+$.

Example 15

Preparation of (1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]hydrazide

a) N-benzyloxycarbonyl-(L)-leucinamide

To a solution of N-benzyloxycarbonyl-L-leucine (3.5 g, 13.2 mmol) in dry THF (40 mL) at -40 °C was added isobutylchloroformate (1.8 g, 13.2 mmol) and N-methylmorphiline (2.8 g, 27.7mmol). After 15 minutes of stirring, ammonia was bubbled through the mixture for an additional 15 minutes, then warmed to room temperature and allowed to stir for 2 hours. The mixture was filtered and the filtrate concentrated in vacuo to yield title compound as a white solid (3.2 g, 92%). MS (ESI): 265.2 $(M+H)^+$.

b) N-benzyloxycarbonyl-L-leucinethioamide

To a stirring solution of the compound of Example 15(a) (3.2 g, 12.4 mmol) in dry THF (50 mL) was added Lawesson's reagent (3.0 g, 7.46 mmol) and the mixture was stirred at room temperature under argon overnight. The solvent was evaporated and the residue

purified by column chromatography (silica gel, ethyl acetate/hexane) to give the title compound as a white solid (3.21 g, 92%). MS (ESI): 281.1 $(M+H)^+$.

c) (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboethoxythiazol-2-yl)-3-methylbutane

The compound of Example 15(b) (3.21 g, 11.5 mmol) was stirred in dry acetone (100 mL) under argon at -10 °C. Ethylbromopyruvate (2.5 g, 12.6 mmol) was added and stirred for 1h at -10 °C. The solution was poured into a well stirred mixture of chloroform and water and then into saturated sodium bicarbonate solution. The organic phase was separated and the aqueous layer extracted with chloroform. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to an oil. The oily residue was treated with TFAA (2.6 g, 12.6 mmol) and pyridine (2.0 g, 25.3 mmol) in dichloromethane for 1h at -20 °C. Excess solvent was removed in vacuo and the residue was dissolved in dichloromethane. The solution was washed with saturated aqueous sodium bicarbonate and 1.0N $KHSO_4$ until pH 7 was reached. The solution was dried ($MgSO_4$), filtered and concentrated to an oil which was purified by column chromatography (silica gel, ethyl acetate/hexane) to give the title compound as a white solid (3.59 g, 83%). MS (ESI): 377.2 $(M+H)^+$.

d) (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane

Following the procedure of Example 1(e), except substituting (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboethoxythiazol-2-yl)-3-methylbutane for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as an off-white solid (3.2 g, 100%). MS (ESI): 349.3 $(M+H)^+$.

e) 2-benzyloxybromobenzene

To a stirring solution of 2-bromophenol (10.0 g, 57.8 mmol), and benzyl bromide (9.9 g, 57.8 mmol) in acetone (150 mL) was added K_2CO_3 (12.0 g, 86.7 mmol). After stirring at reflux for 4h, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a colorless oil (15.2 g, 57.8 mmol). ^{1}HNMR (400 MHz, $CDCl_3$) β

7.62 (m, 1H), 7.54 (m, 2H), 7.45 (m, 2H), 7.37 (m, 1H), 7.28 (m, 1H), 6.98 (m, 1H), 6.91 (m, 1H), 5.17 (s, 2H).

f) 2-benzyloxyphenylboronic acid

To a stirring solution of the compound of Example 15(e) (15.2 g, 57.8 mmol) in THF (100 mL) at -78 °C was added dropwise *n*-BuLi (23.1 mL, 2.5M in hexane, 57.8 mmol). The mixture stirred at -78 °C for 25 min when added via cannulation to a stirring solution of triisopropylborate (54.4 g, 289 mmol) in THF (100 mL) at -78 °C. After warming to room temperature and stirring for 3h, the mixture was poured into 3N HCl (100 mL) and extracted with ethyl acetate (3 x 200 mL). The organic layers were combined, washed successively with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a pale yellow solid (6.9 g, 52%). ^{1}HNMR (400 MHz, $CDCl_3$) β 7.90 (d, 1H), 7.42 (m, 6H), 7.07 (t, 1H), 7.02 (d, 1H), 6.05 (s, 2H), 5.16 (s, 2H).

g) ethyl 2-(2-benzyloxyphenyl)thiazole-4-carboxylate

To a stirring solution of the compound of Example 8(c) (4.0 g, 16.9 mmol), the compound of Example 15(f) (4.29 g, 18.8 mmol), tetrakis(triphenylphosphine)palladium(0) (0.65 g, 0.57 mmol) in dimethoxyethane (60 mL) was added cesium fluoride (8.58 g, 56.5 mmol) and the mixture was heated at 85 °C for 16 h. Tetrakis(triphenylphosphine)palladium(0) (0.65 g, 057 mmol) was added and heating at 85 °C was continued for 5 h. The mixture was diluted with water (60 mL) and extracted with ethyl acetate (2 x 120 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on 180 g of 230-400 mesh silica gel, eluting with 15% ethyl acetate in hexanes, to provide the title compound as a white solid (3.22 g, 56%). MS (ESI): 340.3 $(M+H)^+$.

h) 2-(2-benzyloxyphenyl)thiazol-4-ylcarbonylhydrazide

Following the procedure of Example 1(j), except substituting ethyl 2-(1-naphthyl)thiazole-4-carboxylate for ethyl 2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazole-4-carboxylate, the title compound was prepared as a white solid (2.02 g, 87%). MS (ESI): 326.2 $(M+H)^+$.

i) (1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting 2-(2-benzyloxyphenyl)thiazol-4-ylcarbonylhydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.171 g, 73%). MS (ESI): 656.1 $(M+H)^+$.

Example 16

Preparation of (1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting 2-(1-naphthyl)thiazole-4-carbohydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.130 g, 60%). MS (ESI): 600.4 $(M+H)^+$.

Example 17

Preparation of (1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane for N-(6-methyl-3-

pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.176 g, 84%). MS (ESI): 583.3 $(M+H)^+$.

Example 18

Preparation of (1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-[N-methyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(g)-1(k), except substituting N-cyclopropyl-N-(2-methylpropyl)amine for N-cyclopropylmethylcyclopropylamine in step (g), and (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine in step (k), the title compound was prepared as a white solid (0.177 g, 88%). MS (ESI): 559.2 $(M+H)^+$.

Example 19

Preparation of N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(a)-1(k), except substituting 5-butylpicolinic acid for methyl 6-methylnicotinate in step (a), and L-leucine methyl ester for L-β-*tert*-butylalanine methyl ester in step (c), the title compound was prepared as a white solid (110 mg, 73%). MS (ESI): 557.4 $(M+H)^+$.

Example 20

Preparation of N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(a)-1(k), except substituting 5-butylpicolinic acid for methyl 6-methylnicotinate in step (a), L-leucine methyl ester for L-β-*tert*-butylalanine methyl ester in step (c), and N-cyclopropyl-N-(2-methylpropyl)amine for N-

cyclopropylmethylcyclopropylamine in step (g), the title compound was prepared as a white solid (128 mg, 45%). MS (ESI): 559.3 $(M+H)^+$.

Example 21

Preparation of N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(4-trofluoromethylphenyl)nicotinoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-(4-trofluoromethylphenyl)nicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.164 g, 78%). MS (ESI): 648.1 $(M+H)^+$.

Example 22

Preparation of N-[N-(6-methylpicolinoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-methylpicolinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.108 g, 66%). MS (ESI): 502.2 $(M+H)^+$.

Example 23

Preparation of N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-

cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-(2-pyridinyl)benzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.084 g, 46%). MS (ESI): 564.2 $(M+H)^+$.

Example 24

Preparation of N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(a)-1(e) and 1(k), except substituting 5-butylpicolinic acid for methyl 6-methylnicotinate in step (a), L-leucine methyl ester for L-β-*tert*-butylalanine methyl ester in step (c), and 2-(1-naphthyl)thiazole-4-carbohydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide in step (k), the title compound was prepared as a white solid (0.141 g, 75%). MS (ESI): 574.2 $(M+H)^+$.

Example 25

Preparation of N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-(6-phenyldicotinoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-phenylnicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (0.095 g, 52%). MS (ESI): 564.2 $(M+H)^+$.

Example 26

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-β-*tert*-butylalanyl]hydrazide

a) N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanine

L-β-*tert*-butyl alanine (300 mg, 2.06 mmol) was dissolved in dioxane (4 mL), water (2 mL) and a solution of 1N sodium hydroxyde (2 mL) and taken to 0°C. Di-*tert*-butyl dicarbonate (495 mg, 2.27 mmol) was added and the mixture was allowed to stir at room temperature for two hours. The solution was then concentrated and redissolved in water (5 mL) and ethyl acetate was added. The aqueous phase was acidified to reach pH 3 with 0.3 N $KHSO_4$, then extracted twice with ethyl acetate. The combined organic layers were washed with water, dried ($MgSO_4$), filtered and concentrated to give the title compound as a colorless oil.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(g)-1(k), except substituting N-cyclopropyl-N-(2-methylpropyl)amine for N-cyclopropylmethylcyclopropylamine in step (g), and N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanine for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine in step (k), the title compound was prepared as a white solid (1.2 g, 76%). MS (ESI): 482.3 $(M+H)^+$.

c) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-*tert*-butylalanyl)hydrazide

Following the procedure of Example 2(f), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanyl]hydrazide for N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide, the title compound was prepared as a white solid (0.95 g, 100%). MS (ESI): 382.3 $(M+H)^+$.

d) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-*tert*-butylalanyl)hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-phenylnicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 77%). MS (ESI): 563.2 $(M+H)^+$.

Example 27

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-*tert*-butylalanyl)hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-(2-pyridinyl)benzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (53 mg, 38%). MS (ESI): 563.2 $(M+H)^+$.

Example 28

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(a)-1(k), except substituting methyl 2-methylnicotinate acid for methyl 6-methylnicotinate in step (a) and N-cyclopropyl-N-(2-methylpropyl)amine for N-cyclopropylmethylcyclopropylamine in step (g), the title compound was prepared as a white solid (125 mg, 89%). MS (ESI): 531.2 $(M+H)^+$.

Example 29

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(b)-1(k), except substituting 2-pyridylcarbinol for methyl 6-methyl-3-pyridinylcarbinol in step (d) and N-cyclopropyl-N-(2-methylpropyl)amine for N-cyclopropylmethylcyclopropylamine in step (g), the title compound was prepared as a white solid (100 mg, 54%). MS (ESI): 517.2 $(M+H)^+$.

Example 30

Preparation of (1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(2-chlorophenoxymethyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(j)-1(k), except substituting ethyl 2-(2-chlorophenoxymethyl)thiazole-4-carboxylate for ethyl 2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazole-4-carboxylate in step (j) and (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine in step (k), the title compound was prepared as a white solid (0.016 g, 56%). MS (ESI): 614.2 $(M+H)^+$.

Example 31

Preparation of N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(c)-1(k), except substituting L-leucine methyl ester hydrochloride for L-β-*tert*-butylalanine methyl ester hydrochloride in step (c), 2-pyridylcarbinol for methyl 6-methyl-3-pyridinylcarbinol in step (d), and cyclohexylamine for cyclopropyolamine and isobutyraldehyde for cyclopropanecarboxaldehyde in step (f), the title compound was prepared as a white solid (95 mg, 62%). MS (ESI): 531.2 $(M+H)^+$.

Example 32

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(a)-1(k), except substituting N-cyclopropyl-N-(2-methylpropyl)amine for N-cyclopropylmethylcyclopropylamine in step (g), the title compound was prepared as a white solid (110 mg, 75%). MS (ESI): 531.3 $(M+H)^+$.

Example 33

Preparation of N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-cyclopropylmethylcyclopropylamine for N-cyclopropyl-N-(2-methylpropyl)amine in step (e), the title compound was prepared as a white solid (75 mg, 49%). MS (ESI): 547.3 $(M+H)^+$.

Example 34

Preparation of N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-cyclopropylmethylcyclopropylamine for N-cyclopropyl-N-(2-methylpropyl)amine in step (e) and 4-(2-pyridinyl)benzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (135 mg, 70%). MS (ESI): 547.3 $(M+H)^+$.

Example 35

Preparation of N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-cyclopropylmethylcyclopropylamine for N-cyclopropyl-N-(2-methylpropyl)amine in step (e) and 5-butylpicolinic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (100 mg, 61%). MS (ESI): 527.4 $(M+H)^+$.

Example 36

Preparation of N-[N-(5-butylpicolinoyl)-L-β-cyclopropylalanyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide

a) (S)-2-*tert*-butoxycarbonylaminopent-4-enoic acid

Following the procedure of Example 26(a), except substituting (S)-2-amino-4-pentenoic acid for L-β-*tert*-butyl alanine, the title compound was prepared as a white solid (10.11 g, 86%). MS(ESI): 453.2 $(2M+Na)^+$.

b) N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine methyl ester

To a stirring solution of the compound of Example 36(a) (7.81 g, 36.3 mmol) in ether (100 mL) at 0 °C was added a solution of diazomethane (made from 10 eq. of 1-methyl-3-nitro-1-nitrosoguanidine in ether (500 mL) and 40% NaOH (500 mL) at 0 °C). After stirring for 10 min., $Pd(OAc)_2$ (0.300 g) was added to the solution. After 20min., the solution was concentrated and the residue was filtered through a short plug of silica gel to remove unused catalyst. Concentration of the solution yielded the title compound as a golden yellow oil (8.29 g, 99%). ^1H NMR (400 MHz, $CDCl_3$) β 5.17 (d, 1H), 4.39 (m, 1H), 3.73 (s, 3H), 1.66 (t, 2H), 1.44 (s, 9H), 0.68 (m, 1H), 0.49 (m, 2H), 0.08 (m, 2H).

c) N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine

Following the procedure of Example 1(e), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine methyl ester for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as a tan oil (1.2 g, 17%). MS (ESI): 481.4 $(2M+Na)^+$.

d) N-[N-(5-butylpicolinoyl)-L-β-cyclopropylalanyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-cyclopropylmethylcyclopropylamine for N-cyclopropyl-N-(2-methylpropyl)amine and N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-butylpicolinic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (130 mg, 76%). MS (ESI): 525.3 $(M+H)^+$.

Example 37

Preparation of N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-cyclopropylmethylcyclopropylamine for N-cyclopropyl-N-(2-methylpropyl)amine and N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-(2-pyridinyl)benzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (96 mg, 70%). MS (ESI): 545.3 $(M+H)^+$.

Example 38

Preparation of N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d) and 4-methylimidazole-5-carboxylic

acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (80 mg, 79%). MS (ESI): 504.3 $(M+H)^+$.

Example 39

Preparation of N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d) and 5-butylpicolinic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (70 mg, 63%). MS (ESI): 557.3 $(M+H)^+$.

Example 40

Preparation of N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-cyclopropylmethylcyclopropylamine for N-cyclopropyl-N-(2-methylpropyl)amine and N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 6-(1-pyrrolyl)nicotinic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (115 mg, 89%). MS (ESI): 534.3 $(M+H)^+$.

Example 41

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-(1-pyrrolyl)nicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine,

the title compound was prepared as a white solid (100 mg, 83%). MS (ESI): 538.2 $(M+H)^+$.

Example 42

Preparation of N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d) and 3,4-dimethoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (80 mg, 81%). MS (ESI): 560.3 $(M+H)^+$.

Example 43

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3,4-dimethoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (110 mg, 95%). MS (ESI): 530.3 $(M+H)^+$.

Example 44

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 6-(1-pyrrolyl)nicotinic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (160 mg, 97%). MS (ESI): 536.3 $(M+H)^+$.

Example 45

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-imidazolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 6-(1-imidazolyl)nicotinic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (42 mg, 36%). MS (ESI): 537.4 $(M+H)^+$.

Example 46

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrazolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 6-(1-pyrazolyl)nicotinic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (110 mg, 96%). MS (ESI): 537.3 $(M+H)^+$.

Example 47

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-*tert*-butylalanyl)hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-(1-pyrrolyl)nicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 76%). MS (ESI): 552.3 $(M+H)^+$.

Example 48

Preparation of N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3,4-difluorobenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (118 mg, 89%). MS (ESI): 534.3 $(M+H)^+$.

Example 49

Preparation of N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3,4-dimethoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (86 mg, 64%). MS (ESI): 558.3 $(M+H)^+$.

Example 50

Preparation of N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methylimidazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (100 mg, 71%). MS (ESI): 502.3 $(M+H)^+$.

Example 51

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(c)-1(k), except substituting L-leucine methyl ester hydrochloride for L-β-*tert*-butylalanine methyl ester hydrochloride in step (c), 2-pyridylcarbinol for 6-methyl-3-pyridylcarbinol in step (d), and cyclobutylamine for cyclopropylamine and isobutyraldehyde for cyclopropanecarboxaldehyde in step (f), the title compound was prepared as a white solid (0.192 g, 83%). MS (ESI): 517.3 $(M+H)^+$.

Example 52

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanyl]hydrazide

a) L-β-cyclopropylalanine methyl ester hydrochloride

Following the procedure of Example 2(f), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine methyl ester for N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide, the title compound was prepared as a white solid (2.2 g, 30%). MS (ESI): 144.0 $(M+H)^+$.

b) N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 1(c)-1(k), except substituting L-β-cyclopropylalanine methyl ester hydrochloride for L-β-*tert*-butylalanine methyl ester hydrochloride in step (c), 2-pyridylcarbinol for 6-methyl-3-pyridylcarbinol in step (d), and cyclobutylamine for cyclopropylamine and isobutyraldehyde for cyclopropanecarboxaldehyde in step (f), the title compound was prepared as a white solid (0.192 g, 83%). MS (ESI): 515.3 $(M+H)^+$.

Example 53

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-methylenedioxybenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3,4-methylenedioxybenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (91 mg, 100%). MS (ESI): 516.3 $(M+H)^+$.

Example 54

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (110 mg, 87%). MS (ESI): 500.3 $(M+H)^+$.

Example 55

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and 3,4-difluorobenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.125 g, 76%). MS (ESI): 522.3 $(M+H)^+$.

Example 56

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and 3,4-dimethoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.148 g, 86%). MS (ESI): 546.4 $(M+H)^+$.

Example 57

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and 4-methylimidazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.092 g, 60%). MS (ESI): 490.3 $(M+H)^+$.

Example 58

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3,4-difluorobenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.095g, 63%). MS (ESI): 520.3 $(M+H)^+$.

Example 59

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3,4-dimethoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.100 g, 64%). MS (ESI): 544.3 $(M+H)^+$.

Example 60

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methylimidazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.076 g, 54%). MS (ESI): 488.4 $(M+H)^+$.

Example 61

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylacetyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-methyl-2-phenyloxazole-4-acetic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.115 g, 69%). MS (ESI): 579.4 $(M+H)^+$.

Example 62

Preparation of N-[N-(benzothiazol-6-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and benzothiazole-6-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.119 g, 70%). MS (ESI): 543.3 $(M+H)^+$.

Example 63

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-trifluoromethylbenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (83 mg, 81%). MS (ESI): 538.3 $(M+H)^+$.

Example 64

Preparation of N-(N-benzothiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and benzothiophene-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (50 mg, 32%). MS (ESI): 526.3 $(M+H)^+$.

Example 65

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and 4-methyl-2-(4-trifluoromethylphenyl)thiazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.168 g, 82%). MS (ESI): 651.4 $(M+H)^+$.

Example 66

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-hydroxymethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-hydroxymethylbenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.098 g, 66%). MS (ESI): 514.4 $(M+H)^+$.

Example 67

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-hydroxymethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-hydroxymethylbenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (90 mg, 86%). MS (ESI): 500.3 $(M+H)^+$.

Example 68

Preparation of N-(N-benzothiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and benzothiazole-6-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (90 mg, 82%). MS (ESI): 552.2 $(M+H)^+$.

Example 69

Preparation of N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-cyclopropylmethylcyclopropylamine for N-cyclopropyl-N-(2-methylpropyl)amine and N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2,3-dihydrobenzofuran-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (98 mg, 85%). MS (ESI): 510.3 $(M+H)^+$.

Example 70

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-indole-2-ylcarbonyl-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-*tert*-butylalanyl)hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and indole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (102 mg, 75%). MS (ESI): 525.4 $(M+H)^+$.

Example 71

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-β-*tert*-butylalanyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-*tert*-butylalanyl)hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 1-methylindole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (65 mg, 70%). MS (ESI): 539.4 $(M+H)^+$.

Example 72

Preparation of N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-trifluoromethoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (70 mg, 56%). MS (ESI): 582.4$(M+H)^+$.

Example 73

Preparation of N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-propyloxybenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclopentylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-propyloxybenzoic

acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (95 mg, 67%). MS (ESI): 556.4(M+H)$^+$.

Example 74

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide

a) 3-(2-pyridinyl)benzoic acid

Following the procedure of Example 4(a)-4(c), except substituting 3-formylbenzene boronic acid (3.2 g, 21.34 mmol) for 4-formylbenzene boronic acid in step (a), the title compound was obtained as a white solid (1.05 g). MS (ESI): 200.1 (M+H)$^+$.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3-(2-pyridinyl)benzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (65 mg, 43%). MS (ESI): 549.4 (M+H)$^+$.

Example 75

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methyl-2-(4-trifluoromethylphenyl)thiazole-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxy-carbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (165 mg, 95%). MS (ESI): 637.4 (M+H)$^+$.

Example 76

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-(2-pyridinyl)benzoyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3-(2-pyridinyl)benzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.019 g, 12%). MS (ESI): 561.4 $(M+H)^+$.

Example 77

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d), N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-methyl-2-phenyloxazole-4-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.150 g, 92%). MS (ESI): 565.4 $(M+H)^+$.

Example 78

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethylbenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-trifluoromethylbenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (103 mg, 88%). MS (ESI): 540.3 $(M+H)^+$.

Example 79

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 2,3-dihydrobenzofuran-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (120 mg, 68%). MS (ESI): 514.3 $(M+H)^+$.

Example 80

Preparation of N-(N-benzothiazol-6-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and benzothiazole-6-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (114 mg, 97%). MS (ESI): 529.4 $(M+H)^+$.

Example 81

Preparation of N-(N-benzothiophen-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and benzothiophene-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-

butylalanine, the title compound was prepared as a white solid (130 mg, 88%). MS (ESI): 528.3 $(M+H)^+$.

Example 82

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-methyl-2-phenyloxazole-4-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (140 mg, 90%). MS (ESI): 553.4 $(M+H)^+$.

Example 83

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and 1-methylindole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.122 g, 78%). MS (ESI): 539.4 $(M+H)^+$.

Example 84

Preparation of N-[2-[N-cyclobutyll-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and 2,3-dihydrobenzofuran-5-carboxylic acid for 6-

phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.064 g, 42%). MS (ESI): 528.3 $(M+H)^+$.

Example 85

Preparation of N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and 5-fluoroindole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.107 g, 68%). MS (ESI): 543.4 $(M+H)^+$.

Example 86

Preparation of N-(N-benzothiophen-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(d)-2(g), except substituting cyclobutylamine for cyclopropylamine in step (d) and benzothiophene2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.130 g, 83%). MS (ESI): 542.4 $(M+H)^+$.

Example 87

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenylimidazol-4-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-methyl-2-phenylimidazole-4-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-

butylalanine, the title compound was prepared as a white solid (75 mg, 62%). MS (ESI): 552.5 $(M+H)^+$.

Example 88

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4,5-trimethoxybenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3,4,5-trimethoxybenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (105 mg, 81%). MS (ESI): 562.4 $(M+H)^+$.

Example 89

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-fluoroindole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 90%). MS (ESI): 529.4 $(M+H)^+$.

Example 90

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-hydroxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-

cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-hydroxyindole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 45%). MS (ESI): 527.2 $(M+H)^+$.

Example 91

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-4-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and indole-4-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.091 g, 60%). MS (ESI): 509.3 $(M+H)^+$.

Example 92

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-5-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and indole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.105 g, 69%). MS (ESI): 509.3 $(M+H)^+$.

Example 93

Preparation of N-(N-benzimidazol-5-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and

benzimidazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.147 g, 95%). MS (ESI): 510.3 $(M+H)^+$.

Example 94

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-fluoroindole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.117 g, 74%). MS (ESI): 527.3 $(M+H)^+$.

Example 95

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methyl-2-phenylthiazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methyl-2-phenylthiazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.088 g, 52%). MS (ESI): 567.3 $(M+H)^+$.

Example 96

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-methyl-2-phenylthiazole-4-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.113 g, 68%). MS (ESI): 551.3 $(M+H)^+$.

Example 97

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyquinolin-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methoxyquinoline-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.088 g, 53%). MS (ESI): 551.3 $(M+H)^+$.

Example 98

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5,6-dimethoxyindole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.097 g, 57%). MS (ESI): 569.4 $(M+H)^+$.

Example 99

Preparation of N-[N-(5-chloroindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-chloroindole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.073 g, 45%). MS (ESI): 543.2 $(M+H)^+$.

Example 100

Preparation of N-(N-benzothiazol-6-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and benzothiazole-6-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.104 g, 66%). MS (ESI): 527.2 $(M+H)^+$.

Example 101

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-flurorbenzimidazol-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-fluorobenzimidazole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.101 g, 64%). MS (ESI): 528.2 $(M+H)^+$.

Example 102

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-quinolin-3-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and quinoline-3-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.111 g, 71%). MS (ESI): 521.3 $(M+H)^+$.

Example 103

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-methoxybenzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.110 g, 68%). MS (ESI): 540.3 $(M+H)^+$.

Example 104

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(7-methoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 7-methoxybenzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.120 g, 74%). MS (ESI): 540.3 $(M+H)^+$.

Example 105

Preparation of N-[N-(5-chlorobenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-chlorobenzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.105 g, 64%). MS (ESI): 544.2 $(M+H)^+$.

Example 106

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethoxybenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-trifluoromethoxybenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (113 mg, 90%). MS (ESI): 556.3 $(M+H)^+$.

Example 107

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 1-methylindole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (125 mg, 91%). MS (ESI): 525.3 $(M+H)^+$.

Example 108

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-methylindole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-

butylalanine, the title compound was prepared as a white solid (63 mg, 49%). MS (ESI): 525.4 $(M+H)^+$.

Example 109

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-methoxyindole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (136 mg, 89%). MS (ESI): 541.3 $(M+H)^+$.

Example 110

Preparation of N-(N-benzofuran-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and benzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (94 mg, 75%). MS (ESI): 512.3 $(M+H)^+$.

Example 111

Preparation of N-[N-(2-chloro-3,4-dimethoxybenzoyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-

cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 2-chloro-3,4-dimethoxybenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (80 mg, 61%). MS (ESI): 566.2 $(M+H)^+$.

Example 112

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-methoxyindole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.079 g, 49%). MS (ESI): 539.3 $(M+H)^+$.

Example 113

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-isoquinolin-3-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and isoquinoline-3-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.096 g, 61%). MS (ESI): 521.2 $(M+H)^+$.

Example 114

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-2-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and

indole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.110 g, 72%). MS (ESI): 509.3 $(M+H)^+$.

Example 115

Preparation of N-(N-benzofuran-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and benzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.099 g, 65%). MS (ESI): 510.3 $(M+H)^+$.

Example 116

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolidinyl)nicotinoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-(1-pyrrolidinyl)nicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (180 mg, 55%). MS (ESI): 542.3 $(M+H)^+$.

Example 117

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methyl-2-phenylthiazol-5-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methyl-2-

phenylthiazole-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (130 mg, 93%). MS (ESI): 569.3 $(M+H)^+$.

Example 118

Preparation of N-[N-(5-chlorobenzofuran-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-chlorobenzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (125 mg, 88%). MS (ESI): 546.1 $(M+H)^+$.

Example 119

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-methoxybenzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (95 mg, 72%). MS (ESI): 542.3 $(M+H)^+$.

Example 120

Preparation of N-(N-benzimidazol-5-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and benzimidazole-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (65 mg, 50%). MS (ESI): 512.3 $(M+H)^+$.

Example 121

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5,6-dimethoxyindole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (77 mg, 48%). MS (ESI): 571.3 $(M+H)^+$.

Example 122

Preparation of N-[N-(5-chloroindole-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-chloroindole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-

butylalanine, the title compound was prepared as a white solid (105 mg, 89%). MS (ESI): 545.2 $(M+H)^+$.

Example 123

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxy-3-methylbenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methoxy-3-methylbenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (110 mg, 98%). MS (ESI): 516.5 $(M+H)^+$.

Example 124

Preparation of N-[N-[2-(2-chlorophenyl)-4-methylthiazol-5-ylcarbonyl]-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 2-(2-chlorophenyl)-4-methylthiazole-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (108 mg, 84%). MS (ESI): 603.2 $(M+H)^+$.

Example 125

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methoxyindole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.035 g, 22%). MS (ESI): 539.2 $(M+H)^+$.

Example 126

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methyl-2-(4-trifluoromethylphenyl)thiazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.125 g, 66%). MS (ESI): 635.3 $(M+H)^+$.

Example 127

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-trifluoromethyl-4-azabenzothiophen-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 6-trifluoromethyl-4-azabenzothiophene-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.094 g, 53%). MS (ESI): 595.2 $(M+H)^+$.

Example 128

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-phenyl-5-trifluoromethyloxazol-4-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 2-phenyl-5-trifluoromethyloxazole-4-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (130 mg, 96%). MS (ESI): 607.2 $(M+H)^+$.

Example 129

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyquinolin-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methoxyquinoline-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (100 mg, 74%). MS (ESI): 553.3 $(M+H)^+$.

Example 130

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methoxy-4,5-methylenedioxybenzoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3-methoxy-4,5-methylenedioxybenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-

butylalanine, the title compound was prepared as a white solid (46 mg, 40%). MS (ESI): 546.3 $(M+H)^+$.

Example 131

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-2-ylcarbonyl-L-leucinyl)hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and indole-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (95 mg, 79%). MS (ESI): 511.3 $(M+H)^+$.

Example 132

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(7-methoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 7-methoxybenzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 76%). MS (ESI): 542.2 $(M+H)^+$.

Example 133

Preparation of N-[N-(3-chlorobenzothiophen-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-

cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3-chlorobenzothiophene-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (120 mg, 92%). MS (ESI): 562.1 $(M+H)^+$.

Example 134

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-6-ylcarbonyl-L-leucinyl)hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and indole-6-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (50 mg, 48%). MS (ESI): 511.3 $(M+H)^+$.

Example 135

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methylthiophene-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3-methylthiophene-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (110 mg, 89%). MS (ESI): 492.3 $(M+H)^+$.

Example 136

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,6-dimethoxynicotinoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2,6-dimethoxynicotinic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.099 g, 62%). MS (ESI): 531.3 $(M+H)^+$.

Example 137

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-pyridinyl)thiophen-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(2-pyridinyl)thiophene-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.103 g, 62%). MS (ESI): 553.2 $(M+H)^+$.

Example 138

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-mercaptopyridinylmethyl)furan-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(2-mercaptopyridinylmethyl)furan-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.129 g, 74%). MS (ESI): 583.3 $(M+H)^+$.

Example 139

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-6-ylcarbonyl-L-leucinyl)hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and indole-6-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (51 mg, 44%). MS (ESI): 511.3 $(M+H)^+$.

Example 140

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-methylthiazol-4-yl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methyl-2-(2-methylthiazol-4-yl)thiazole-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (120 mg, 86%). MS (ESI): 590.2 $(M+H)^+$.

Example 141

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolyl)benzothiazol-6-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 2-(1-pyrrolyl)benzothiazole-6-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-

β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 64%). MS (ESI): 594.4 $(M+H)^+$.

Example 142

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dichlorobenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3,4-dichlorobenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.086 g, 53%). MS (ESI): 538.2 $(M+H)^+$.

Example 143

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methanesulfonylbenzoyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methanesulfonylbenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.116 g, 70%). MS (ESI): 548.1 $(M+H)^+$.

Example 144

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-phenyl-5-trifluoromethyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-phenyl-5-trifluoromethyloxazole-4-carboxylic acid for 6-phenylnicotinic acid in step (g),

the title compound was prepared as a white solid (0.111 g, 61%). MS (ESI): 605.3 $(M+H)^+$.

Example 145

Preparation of N-[N-[2-(2-chlorophenyl)-4-methylthiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(2-chlorophenyl)-4-methylthiazole-5-carboxlyic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.076 g, 41%). MS (ESI): 601.3 $(M+H)^+$.

Example 146

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclohexylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-cyclohexylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3,4-dimethoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (85 mg, 59%). MS (ESI): 572.4 $(M+H)^+$.

Example 147

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-trifluoromethyl-4-azabenzothiophen-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 6-

trifluoromethyl-4-azabenzothiophene-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (130 mg, 94%). MS (ESI): 597.2 $(M+H)^+$.

Example 148

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,6-dimethoxynicotinoyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 2,6-dimethoxynicotinic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 76%). MS (ESI): 533.3 $(M+H)^+$.

Example 149

Preparation of (2S)-N-(N-benzodioxan-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and S-benzodioxane-2-carboxlyic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.080 g, 50%). MS (ESI): 528.2 $(M+H)^+$.

Example 150

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-pyridinyl)thiophen-5-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-

cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 2-(2-pyridinyl)thiophene-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (115 mg, 74%). MS (ESI): 555.2 $(M+H)^+$.

Example 151

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-propionyl-L-leucinyl)hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and propionic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (85 mg, 74%). MS (ESI): 424.3 $(M+H)^+$.

Example 152

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(4-morpholino)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 2-ethoxycarbonylmalondialdehyde

To a stirring mixture of sodium hydride (1.26 g, 31.6 mmol, 60% dispersion in mineral oil) and ethyl formate (19.5 g, 263 mmol) in diethyl ether (100 mL) at 0 βC was added ethyl 3,3-diethoxypropionate (5.0 g, 26.3 mmol) dropwise over 2h. The solution then stirred at 5 βC for 10h and room temperature for 16h. The mixture was poured into cold water and washed with ether. The aqueous layer was acidified to pH of 3 with 10% HCl and extracted with dichloromethane (3x). The organic layers were combined, washed with saturated brine, dried ($MgSO_4$), filtered and concentrated to yield the title compound as a colorless oil (2.4 g, 63%). ^{1}HNMR (400MHz, $CDCl_3$) β 9.08 (s, 2H), 4.31 (s, 1H), 4.18 (q, 2H), 1.23 (t, 3H).

b) ethyl 2-methylthiopyrimidine-5-carboxylate

To a solution of anhydrous sodium acetate (1.5 g, 19.1 mmol) in DMF (90 mL) was added S-methylisothiourea sulfate (2.5 g, 9.1 mmol) followed by the compound of Example 152(a) (2.4 g, 15.4 mmol). After stirring at 85βC for 16h, the mixture was cooled, diluted with water and extracted with diethyl ether (2x). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (1.52 g, 85%). MS (ESI): 199.1 $(M+H)^+$.

c) ethyl 2-methanesulfonylpyrimidine-5-carboxylate

To a stirring solution of the compound of Example 152(b) (0.300 g, 1.52 mmol) in dichloromethane (25 mL) was added *m*-chloroperoxybenzoic acid (0.706 g, 4.1 mmol). After stirring at room temperature for 3h, the solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (0.222 g, 63%). ^{1}HNMR (400MHz, $CDCl_3$) β 9.41 (s, 2H), 4.50 (q, 2H), 3.38 (s, 3H), 1.42 (t, 3H).

d) ethyl 2-(4-morpholino)pyrimidine-5-carboxylate

After stirring for 16h at 100βC, a solution of the compound of Example 152(c) (0.100 g, 0.435 mmol) in morpholine (2 mL) was diluted with ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$), filtered and concentrated to yield the title compound as a white solid (0.068 g, 66%). ^{1}HNMR (400MHz, $CDCl_3$) β 8.81 (s, 2H), 4.31 (q, 2H), 3.89 (t, 4H), 3.72 (t, 4H), 1.32 (t, 3H).

e) 2-(4-morpholino)pyrimidine-5-carboxylic acid

Following the procedure of Example 1(e), except substituting ethyl 2-(4-morpholino)pyrimidine-5-carboxylate for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as a white solid (0.060 g, 100%). MS(ESI): 210.0 $(M+H)^+$.

f) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(4-morpholino)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(4-morpholino)pyrimidine-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.107 g, 70%). MS (ESI): 557.3 $(M+H)^+$.

Example 153

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-methylthiazol-4-yl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methyl-2-(2-methylthiazol-4-yl)thiazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.118 g, 67%). MS (ESI): 588.3 $(M+H)^+$.

Example 154

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolyl)benzothiazol-6-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(1-pyrrolyl)benzothiazole-6-carbonyl acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.107 g, 60%). MS (ESI): 592.3 $(M+H)^+$.

Example 155

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-trifluoromethoxyindol-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-trifluoromethoxyindole-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.096 g, 54%). MS (ESI): 593.2 $(M+H)^+$.

Example 156

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolidino)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 2-(1-pyrrolidino)pyrimidine-5-carboxylic acid

Following the procedure of Example 152(a)-152(e), except substituting pyrrolidine for morpholine in step (d), the title compound was prepared as a white solid (0.057 g, 100%). MS (ESI): 193.9 $(M+H)^+$.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolidino)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(1-pyrrolidino)pyrimidine-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.074 g, 51%). MS (ESI): 541.3 $(M+H)^+$.

Example 157

Preparation of N-(N-butyryl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and butyric acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (130 mg, 87%). MS (ESI): 438.3 $(M+H)^+$.

Example 158

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methylbutyryl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and isovaleric acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (110 mg, 85%). MS (ESI): 452.3 $(M+H)^+$.

Example 159

Preparation of N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-cyclohexylglycinyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-cyclopropylmethylcyclopropylamine for N-cyclopropyl-N-(2-methylpropyl)amine and N-*tert*-butoxycarbonyl-L-cyclohexylglycine for N-*tert*-butoxycarbonyl-L-leucine in step (e), and 3,4-dimethoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (90 mg, 53%). MS (ESI): 556.3 $(M+H)^+$.

Example 160

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-thieno[2,3-b]thiophen-2-ylcarbonyl-L-leucinyl)hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and thieno[2,3-b]thiophene-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (115 mg, 83%). MS (ESI): 534.3 $(M+H)^+$.

Example 161

Preparation of N-[N-(5-*tert*-butyl-3-methylthieno[2,3-b]thiophen-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-*tert*-butyl-3-methylthieno[2,3-b]thiophene-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (140 mg, 85%). MS (ESI): 604.2 $(M+H)^+$.

Example 162

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylic acid

Following the procedure of Example 152(a)-152(e), except substituting N,N,N'-trimethylethylenediamine for morpholine in step (d), the title compound was prepared as a white solid (0.125 g, 100%). MS (ESI): 225.1 $(M+H)^+$.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.073 g, 48%). MS (ESI): 572.3 $(M+H)^+$.

Example 163

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(1,2,3-thiadiazol-5-yloxy)benzoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-(1,2,3-thiadiazol-5-yloxy)benzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (125 mg, 85%). MS (ESI): 572.2 $(M+H)^+$.

Example 164

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

a) 2-hydroxy-4,5-dimethoxybenzaldehyde

To a stirring solution of 2-benzyloxy-4,5-dimethoxybenzaldehyde (1.0 g, 3.67 mmol) in ethyl acetate (25 mL) was added 10% palladium on carbon (0.50 g). The mixture was stirred under a hydrogen atmosphere for 4h, then filtered through Celite. The filtrate was concentrated to yield the title compound as a pale yellow solid (0.632 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) β 11.41 (s, 1H), 9.72 (s, 1H), 6.89 (s, 1H), 6.48 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H).

b) 4,5-dimethoxy-2-ethoxycarbonylmethoxybenzaldehyde

Following the procedure of Example 15(e), except substituting 2-hydroxy-4,5-dimethoxybenzaldehyde for 2-bromophenol and ethyl bromoacetate for benzyl bromide, the title compound was prepared (0.758 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) β 10.39 (s, 1H), 7.30 (s, 1H), 6.41 (s, 1H), 4.72 (s, 2H), 4.22 (q, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 1.26 (t, 3H).

c) ethyl 5,6-dimethoxybenzofuran-2-carboxylate

A mixture of the compound of Example 164(b) (0.758 g, 2.8 mmol) and potassium carbonate (0.975 g, 7.1 mmol) was stirred at 80 βC in DMF (20 mL) for 5h. The mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with water and satruated brine then dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (0.405 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) β 7.45 (s, 1H), 7.10 (s, 1H), 7.04 (s, 1H), 4.41 (q, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 1.41 (t, 3H).

d) 5,6-dimethoxybenzofuran-2-carboxylic acid

Following the procedure of Example 1(e), except substituting ethyl 5,6-dimethoxybenzofuran-2-carboxylate for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as a white solid (0.263 g,

73%). ^{1}H NMR (400 MHz, $CDCl_3$) β 7.40 (s, 1H), 7.03 (s, 1H), 7.01 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H).

e) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5,6-dimethoxybenzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.126 g, 74%). MS (ESI): 570.3 $(M+H)^+$.

Example 165

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-(4-triflouormethylphenyl)oxazol-4-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-(4-triflouormethylphenyl)oxazole-4-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 55%). MS (ESI): 607.3 $(M+H)^+$.

Example 166

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazole-5-carboxylic acid for N-(6-methyl-3-

pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (113 mg, 63%). MS (ESI): 638.2 $(M+H)^+$.

Example 167

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(3-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methyl-2-(3-trifluoromethylphenyl)thiazole-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (142 mg, 95%). MS (ESI): 637.3 $(M+H)^+$.

Example 168

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoyl]-L-β-cyclopropylalanyl]hydrazide

a) methyl 3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoate

To a stirring mixture of sodium hydride (5.8 g, 145 mmol, 60% dispersion in mineral oil) in DMF (80 mL) was added slowly a solution of methyl-3-hydroxy-4-methoxybenzoate (11.0 g, 60 mmol) in DMF (80 mL). After stirring for 30 min, N,N-dimethylaminoethylchloride hydrochloride (9.5 g, 66 mmol) was added slowly. After stirring for 16h at 80 βC, the solution was diluted with saturated brine and extracted with ethyl acetate (2x). The organic layers were combined and washed with water and brine the dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, methanol/dichloromethane) to yield the title compound as an off-white solid (9.45 g, 62%). MS (ESI): 254.2 $(M+H)^+$.

b) 3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoic acid

Following the procedure of Example 1(e), except substituting methyl 3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoate for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as a pale yellow solid (2.39 g, 100%). MS (ESI): 240.2 $(M+H)^+$.

c) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.133 g, 75%). MS (ESI): 586.3 $(M+H)^+$.

Example 169

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) ethyl 5-hydroxybenzofuran-2-carboxylate

To a mixture of aluminum chloride (6.3 g, 47.7 mmol) and ethanethiol (4.5 g, 72.9 mmol) in dichloromethane (81 mL) at 0 βC was added ethyl 5-methoxybenzofuran-2-carboxylate (3.0 g, 13.6 mmol). After stirring for 16h at room temperature, the mixture was poured into water, acidified with 3N HCl and extracted with dichloromethane (2x). The organic layers were combined, washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (2.16 g, 77%). ^1H NMR (400 MHz, $CDCl_3$) β 7.45 (m, 2H), 7.08 (m, 1H), 7.02 (m, 1H), 5.35 (s b, 1H), 4.44 (q, 2H), 1.42 (t, 3H).

b) ethyl 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylate

To a solution of the compound of Example 169(a) (0.200 g 0.971 mmol), 4-(2-hydroxyethyl)morpholine (0.165 g, 1.26 mmol), and triphenylphosphine (0.331 g, 1.26 mmol) in THF (4 mL) at 0 βC was added dropwise diisopropylazodicarboxylate (0.254 g, 1.26 mmol). After stirring at room temperature for 16h, the solution was concentrated and purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (0.235 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) β 7.48 (m, 2H), 7.07 (m, 2H), 4.43 (q, 2H), 4.14 (m, 2H), 3.76 (m, 4H), 2.86 (m, 2H), 2.61 (m, 4H), 1.40 (t, 3H).

c) 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid

Following the procedure of Example 1(e), except substituting ethyl 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylate for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as a white solid (0.150 g, 70%). MS (ESI): 292.1 $(M+H)^+$.

d) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.141 g, 73%). MS (ESI): 639.3 $(M+H)^+$.

Example 170

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-thienyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 4-methyl-2-(2-thienyl)thiazole-5-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-

butylalanine, the title compound was prepared as a white solid (126 mg, 77%). MS (ESI): 575.2 $(M+H)^+$.

Example 171

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (60 mg, 20%). MS (ESI): 589.4 $(M+H)^+$.

Example 172

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid

Following the procedure of Example 169(a)-169(c), except substituting 2-dimethylaminoethanol for 4-(2-hydroxyethyl)morpholine in step (b), the title compound was prepared as a white solid (0.139 g, 100%). ^1H NMR (400 MHz, $CDCl_3$) β 7.36 (d, 1H), 7.12 (m, 2H), 7.00 (d, 1H), 4.32 (t, 2H), 3.56 (t, 2H), 2.95 (s, 6H).

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid for 6-phenylnicotinic acid

in step (g), the title compound was prepared as a white solid (0.131 g, 73%). MS (ESI): 597.3 $(M+H)^+$.

Example 173

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(1-piperidinyl)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid

Following the procedure of Example 169(a)-169(c), except substituting 2-(1-piperidinyl)ethanol for 4-(2-hydroxyethyl)morpholine in step (b), the title compound was prepared as a white solid (0.185 g, 100%). MS (ESI): 290.1 $(M+H)^+$.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(1-piperidinyl)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.131 g, 68%). MS (ESI): 637.4 $(M+H)^+$.

Example 174

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-thieno[2,3-b]thiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and thieno[2,3-b]thiophene-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.089 g, 56%). MS (ESI): 532.3 $(M+H)^+$.

Example 175

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazole-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.142 g, 74%). MS (ESI): 636.2 $(M+H)^+$.

Example 176

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5,6-dimethoxybenzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (90 mg, 64%). MS (ESI): 572.3 $(M+H)^+$.

Example 177

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(4-morpholino)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 2-methylthiopyrimidine-4-carboxylic acid potassium salt

To a suspension of 5-bromo-2-methylthiopyrimidine-4-carboxylic acid (1.25 g, 5.0 mmol) in methanol (60 mL) in a Parr bottle was added potassium hydroxide (0.630 g, 11.2 mmol) following by 10% palladium on $BaSO_4$ (0.630 g, 50% w/w). After shaking under

hydrogen on a Parr shaker at 35 psi for 3h, the mixture was filtered through Celite. The filtrate was concentrated to yield the title compound without any further isolation. ^{1}H NMR (400 MHz, MeOH-*d*) β 8.59 (d, 1H), 7.48 (d, 1H), 2.60 (s, 3H).

b) ethyl 2-methylthiopyrimidine-4-carboxylate

Following the procedure of Example 8(c), except substituting 2-methylthiopyrimidine-4-carboxylic acid potassium salt for 2-bromothiazole-4-carboxylic acid, the title xompound was prepared as an oily yellow solid (0.851 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) β 8.72 (d, 1H), 7.58 (d, 1H), 4.44 (q, 2H), 2.62 (s, 3H), 1.45 (t, 3H).

c) 2-(4-morpholino)pyrimidine-4-carboxylic acid

Following the procedure of Example 152(c)-152(e), except substituting ethyl 2-methylthiopyrimidine-4-carboxylate for ethyl 2-methylthiopyrimidine-5-carboxylate in step (c), the title compound was prepared as a white solid (0.125 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) β 8.48 (d, 1H), 7.17 (d, 1H), 3.82 (t, 4H), 3.72 (t, 4H).

d) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(4-morpholino)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(4-morpholino)pyrimidine-4-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.132 g, 79%). MS (ESI): 557.4 $(M+H)^+$.

Example 178

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylic acid

Following the procedure of Example 152(c)-152(e), except substituting ethyl 2-methylthiopyrimidine-4-carboxylate for ethyl 2-methylthiopyrimidine-5-carboxylate in step

(c) and 4-*tert*-butoxycarbonylpiperazine in dichloromethane for morpholine in step (d), the title compound was prepared as a white solid (0.258 g, 99%). MS (ESI): 309.3 $(M+H)^+$.

b) N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.137 g, 69%). MS (ESI): 656.4 $(M+H)^+$.

c) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(f), except substituting N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide for N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide, the title compound was prepared as a white solid (0.079 g, 68%). MS (ESI): 556.2 $(M+H)^+$.

Example 179

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-piperazinyl)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylic acid

Following the procedure of Example 152(a)-152(e), except substituting N-*tert*-butoxycarbonylpiperazine in dichloromethane for morpholine in step(d), the title compound was prepared as a white solid (0.330 g, 96%). MS (ESI): 309.4 $(M+H)^+$.

b) N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-5-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.138 g, 70%). MS (ESI): 656.4 $(M+H)^+$.

c) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-piperazinyl)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(f), except substituting N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-5-ylcarbonyl]hydrazide for N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide, the title compound was prepared as a white solid (0.056 g, 48%). MS (ESI): 556.3 $(M+H)^+$.

Example 180

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (20 mg, 15%). MS (ESI): 599.2 $(M+H)^+$.

Example 181

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(1-piperidinyl)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide

a) 7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid

Following the procedure of Example 169(a)-169(c), except substituting ethyl 7-methoxybenzofuran-2-carboxylate for ethyl 5-methoxybenzofuran-2-carboxylate in step (a) and 2-(1-piperidinyl)ethanol for 4-(2-hydroxyethyl)morpholine in step (b), the title compound was prepared as a white solid. MS (ESI): 290.2 $(M+H)^+$.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(1-piperidinyl)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (60 mg, 35%). MS (ESI): 639.4 $(M+H)^+$.

Example 182

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide

a) 7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid

Following the procedure of Example 169(a)-169(c), except substituting ethyl 7-methoxybenzofuran-2-carboxylate for ethyl 5-methoxybenzofuran-2-carboxylate in step (a) and 2-(N,N-dimethylamino)ethanol for 4-(2-hydroxyethyl)morpholine in step (b), the title compound was prepared (350 mg, 100%). MS (ESI): 250.1 $(M+H)^+$.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (25 mg, 16%). MS (ESI): 599.4 $(M+H)^+$.

Example 183

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

a) 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-4-carboxylic acid

Following the procedure of Example 177(a)-177(c), except substituting N,N,N'-trimethylethylenediamine for morpholine in step (c), the title compound was prepared as a white solid (0.182 g, 99%). MS (ESI): 225.1 $(M+H)^+$.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-4-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.127 g, 74%). MS (ESI): 572.5 $(M+H)^+$.

Example 184

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]- N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

a) 2-(1-naphthyl)thiazole-4-carboxylic acid

Following the procedure of Example 1(e), except substituting ethyl 2-(1-naphthyl)thiazole-4-carboxylate for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as an off-white solid (0.359 g, 100%). MS (ESI): 256.0 $(M+H)^+$.

b) N N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]- N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 15(e)-15(i), except substituting the compound of Example 2-(1-naphthyl)thiazole-4-carboxylic acid for (1S)-1-(benzyloxycarbonyl)amino-1-(4-carboxythiazol-2-yl)-3-methylbutane, the title compound was prepared as a white solid (0.078 g, 82%). MS (ESI): 563.2 $(M+H)^+$.

Example 185

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.071 g, 40%). MS (ESI): 597.5 $(M+H)^+$.

Example 186

Preparation of N-[N-(5-carboxymethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

a) benzyl 5-hydroxybenzofuran-2-carboxylate

A solution of the compound of Example 169(a) (0.200 g, 0.907 mmol) and lithium hydroxide monohydrate (0.045 g, 1.07 mmol) in THF (3 mL) and water (3 mL) was stirred at reflux for 2h. The solution was concentrated to a pale yellow solid and dissolved in benzyl alcohol (5 mL) and concentrated HCl (1 mL). After stirring at 100 βC for 24h, the solution was diluted with ethyl acetate and washed successively with saturated aqueous $NaHCO_3$, water and saturated brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (0.094 g, 39%). ^1H NMR (400 MHz, $CDCl_3$) β 7.43 (m, 7H), 7.06 (d, 1H), 7.00 (dd, 1H), 5.40 (s, 2H).

b) benzyl 5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylate

Following the procedure of Example 15(e), except substituting benzyl 5-hydroxybenzofuran-2-carboxylate for 2-bromophenol and *tert*-butyl bromoacetate for benzyl bromide, the title compound was prepared (0.134 g, 100%). ^{1}HNMR (400 MHz, $CDCl_3$) β 7.44 (m, 4H), 7.36 (m, 3H), 7.12 (dd, 1H), 7.02 (d, 1H), 5.38 (s, 2H), 4.52 (s, 2H), 1.48 (s, 9H).

c) 5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid

Following the procedure of Example 164(a), except substituting benzyl 5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylate for 2-benzyloxy-4,5-dimethoxybenzaldehyde, the title compound was prepared as a pale yellow solid (0.102 g, 100%). ^{1}HNMR (400 MHz, $CDCl_3$) β 7.40 (m, 2H), 7.04 (dd, 1H), 6.98 (d, 1H), 4.50 (s, 2H), 1.41 (s, 9H).

d) N-[N-(5-*tert*-butoxycarbonylmethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and 5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.170 g, 81%). MS (ESI): 640.4 $(M+H)^+$.

e) N-[N-(5-carboxymethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 2(f), except substituting N-[N-(5-*tert*-butoxycarbonylmethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide for N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide, the title compound was prepared as a white solid (0.128 g, 83%). MS (ESI): 584.3 $(M+H)^+$.

Example 187

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide

a) 7-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid

Following the procedure of Example 169(a)-169(c), except substituting ethyl 7-methoxybenzofuran-2-carboxylate for ethyl 5-methoxybenzofuran-2-carboxylate in step (a), the title compound was prepared as a white solid. MS (ESI): 292.3 $(M+H)^+$.

b) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 7-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid for N-(6-methyl-3-

pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (65 mg, 34%). MS (ESI): 641.4 $(M+H)^+$.

Example 188

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3,4-(1,3-propylenedioxy)benzoyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 3,4-(1,3-propylenedioxy)benzoic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (100 mg, 61%). MS (ESI): 543.9 $(M+H)^+$.

Example 189

Preparation of N-[N-(7-carboxymethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 186(a)-186(e), except substituting ethyl 7-hydroxybenzofuran-2-carboxylate for ethyl 5-hydroxybenzofuran-2-carboxylate in step (a), the title compound was prepared as a white solid (0.076 g, 55%). MS (ESI): 584.3 $(M+H)^+$.

Example 190

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-(3-triflouormethylphenyl)oxazol-4-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-(3-

triflouormethylphenyl)oxazole-4-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (105 mg, 37%). MS (ESI): 607.1 $(M+H)^+$.

Example 191

Preparation of N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide

Following the procedure of Example 1(k), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[L-leucinyl]hydrazide for N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide and 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine, the title compound was prepared as a white solid (150 mg, 48%). MS (ESI): 641.2 $(M+H)^+$.

Example 192

Preparation of N-[N-(5-carboxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazidea) 4-benzyloxycarbonylmethoxy-3-formylbenzyaldehyde

To a mixture of 5-formylsalicylaldehyde (2.2 g, 14.7 mmol) and potassium bromide (5.0 g, 36.8 mmol) in acetone (50 mL) was added benzyl bromoacetate (4.8 g, 16.1 mmol). After stirring at reflux for 6h, the mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to yield the title compound (4.13 g, 94%). ^1H NMR (400 MHz, $CDCl_3$) β 10.56 (s, 1H), 9.95 (s, 1H), 8.38 (s, 1H), 8.07 (d, 1H), 7.38 (m, 5H), 6.95 (d, 1H), 5.26 (s, 2H), 4.91 (s, 2H).

b) benzyl 5-formylbenzofuran-2-carboxylate

Following the procedure of Example 164(c), except substituting 4-benzyloxycarbonylmethoxy-3-formylbenzyaldehyde for 4,5-dimethoxy-2-ethoxycarbonylmethoxybenzaldehyde, the title compound was prepared as a white solid

(1.78 g, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) β 10.09 (s, 1H), 8.24 (s, 1H), 8.05 (d, 1H), 7.71 (d, 1H), 7.68 (s, 1H), 7.42 (m, 5H), 5.43 (s, 2H).

c) benzyl 5-carboxybenzofuran-2-carboxylate

To a solution of the compound of Example 192(b) (0.380 g, 0.1.36 mmol) in THF (5 mL) and *t*-butanol (1 mL) was added slowly a solution of sodium chlorite (0.245 g 2.71 mmol) and sulfamic acid (0.277 g, 2.86 mmol) in water (2 mL). After stirring at room temperature for 3h, the solution was partitioned between ethyl acetate and water. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate, and saturated brine then dried ($MgSO_4$), filtered and concentrated to yield the title compound as an off-white solid (0.272 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) β 8.52 (s, 1H), 8.23 (d, 1H), 7.67 (m, 2H), 7.49 (m, 2H), 7.41 (m, 3H), 5.46 (s, 2H).

d) benzyl 5-methoxycarbonylbenzofuran-2-carboxylate

To a solution of the compound of Example 192(c) (0.214 g, 0.723 mmol) in diethyl ether (20 mL) at 0 βC was added dropwise diazomethane until a yellow color persists after 5 min. of stirring. The solution was then concentrated and the residue purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a white solid (0.219 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) β 8.45 (s, 1H), 8.17 (d, 1H), 7.65 (m, 2H), 7.50 (m, 2H), 7.40 (m, 2H), 7.27 (s, 1H), 5.46 (s, 2H), 3.97 (s, 3H).

e) 5-methoxycarbonylbenzofuran-2-carboxylic acid

Following the procedure of Example 164(a), except substituting benzyl 5-methoxycarbonylbenzofuran-2-carboxylate for 2-benzyloxy-4,5-dimethoxybenzaldehyde, the title compound was prepared as a white solid (0.152 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) β 8.41 (s, 1H), 8.12 (dd, 1H), 7.60 (m, 2H), 3.94 (s, 3H).

f) N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxycarbonylbenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide

Following the procedure of Example 2(e)-2(g), except substituting N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine for N-*tert*-butoxycarbonyl-L-leucine in step (e) and

5-methoxycarbonylbenzofuran-2-carboxylic acid for 6-phenylnicotinic acid in step (g), the title compound was prepared as a white solid (0.102 g, 55%). MS (ESI): 568.1 $(M+H)^+$.

g) N-[N-(5-carboxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 1(e), except substituting N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxycarbonylbenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide for N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester, the title compound was prepared as an off-white solid (0.023 g, 23%). MS (ESI): 554.2 $(M+H)^+$.

Example 193

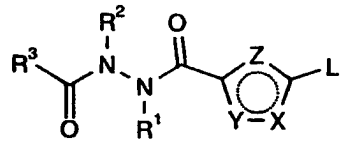
Preparation of N-[N-(7-carboxymethoxybenzofuran-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide

Following the procedure of Example 186(a)-186(e), except substituting ethyl 7-hydroxybenzofuran-2-carboxylate for ethyl 5-hydroxybenzofuran-2-carboxylate in step (a) and N-*tert*-butoxycarbonyl-L-leucine for N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine in step (d), the title compound was prepared as a white solid (55 mg, 86%). MS (ESI): 586.1 $(M+H)^+$.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

We claim:

1. A compound of Formula I:



I

wherein:

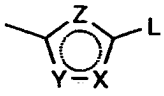
L is selected from the group consisting of:C_{2-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $CH(R^4)NR^5R^6$, $CH(R^4)Ar$, $CH(R^4)OAr'$, and NR^4R^7;

X, Y, Z are independently selected from the group consisting of: N, O, S and CR^{10}, provided that at least two of X, Y and Z are heteroatoms and at least one of X, Y and Z is N, or one of X, Y and Z is C=N, C=C or N=N and the other two are CR^{10} or N, provided that X, Y and Z together comprise at least two N;

– indicates a single or double bond in the five-membered heterocycle;

R', R^1, R^2, R^5, R^{10}, R^{12}, R^{16} and R^{17} are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^3 is selected from the group consisting of: C_{3-6}alkyl, Ar, Het, $CH(R^{11})Ar$, $CH(R^{11})OAr$, $NR^{11}R^{12}$, $CH(R^{11})NR^{12}R^{13}$; and



;

R^4, R^{11}, and R^{15} are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-11}cycloalkyl-C_{0-6}-alkyl, Ar-C_{0-6}alkyl, Ar-C_{2-6}alkenyl, Ar-C_{2-6}alkynyl, Het-C_{0-6}alkyl, Het-C_{2-6}alkenyl, Het-C_{2-6}alkynyl, C_{1-6}alkyl, optionally substituted by OR^8, SR^8, NR^8R^9, $N(R')CO_2R'$, CO_2R', $CONR^{10}R^{11}$, and $N(C=NH)NH_2$;

R^6 and R^{13} are independently selected from the group consisting of: R^{14}, $R^{14}C(O)$, $R^{14}C(S)$, $R^{14}OC(O)$, and $R^{14}OC(O)NR^9CH(R^{15})(CO)$;

R^7 is selected from the group consisting of: C_{1-6}alkyl, C_{1-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}-alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^4 and R^7 may be combined to form a 3-7 membered monocyclic or 7-10-membered bicyclic carbocyclic or heterocyclic ring, optionally substituted with 1-4 of C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkoxy, Ar-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}NR^8R^9$, $O(CH_2)_{1-6}NR^8R^9$;

$R^8$and R^9 are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, and $R^{16}R^{17}NC_{2-6}$alkyl;

R^{14} is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

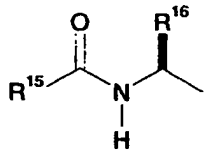
and pharmaceutically acceptable salts, hydrates and solvates thereof.

2. A compound according to Claim 1 wherein R^1 and R^2 are H.

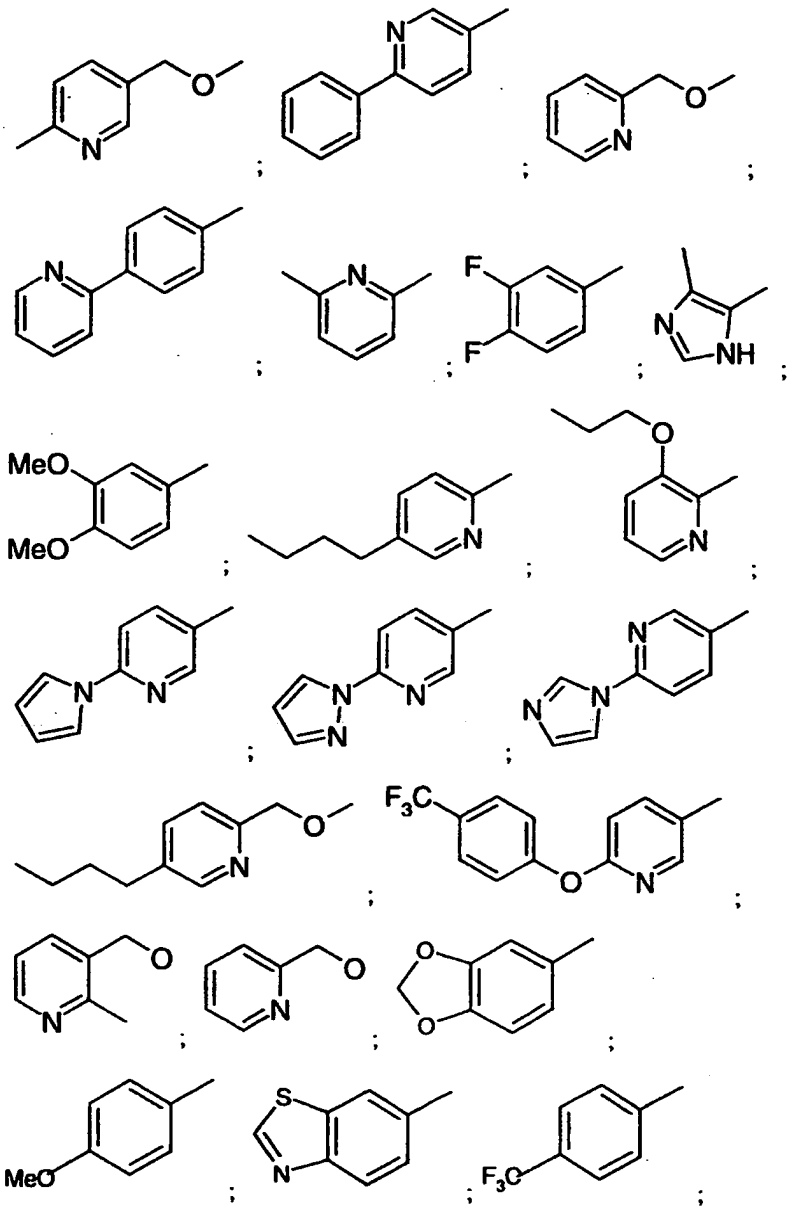
3. A compound according to Claim 1 wherein X is S, Y is CH, and Z is N.

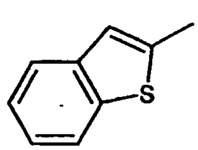
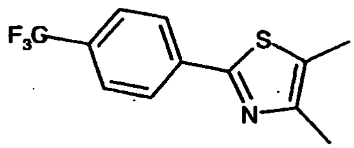
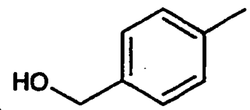
4. A compound according to Claim 1 wherein:

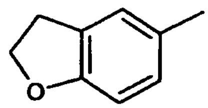
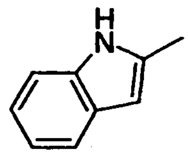
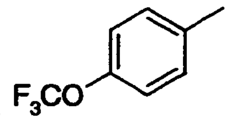
R^3 is preferably:

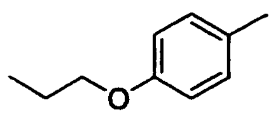
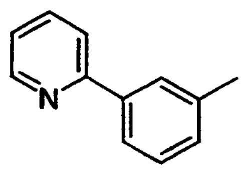
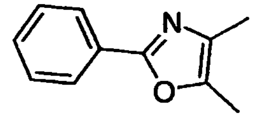


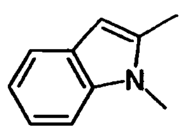
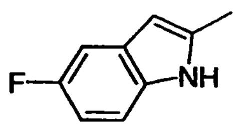
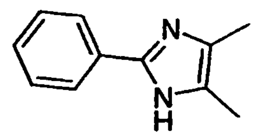
wherein R^{15} is independently selected from the group consisting of:

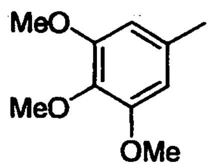
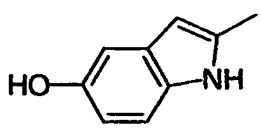
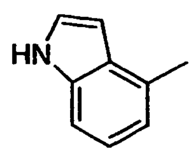


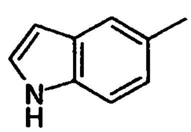
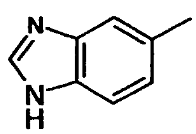
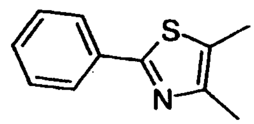
 ;  ;  ;

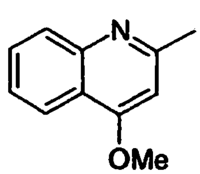
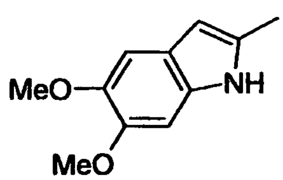
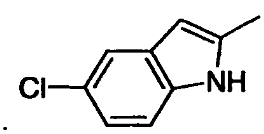
 ;  ;  ;

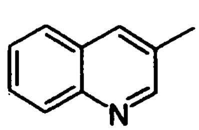
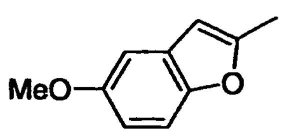
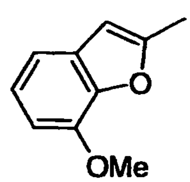
 ;  ;  ;

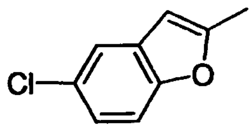
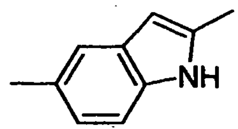
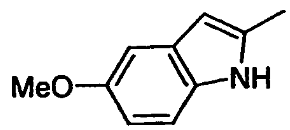
 ;  ;  ;

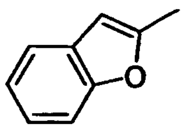
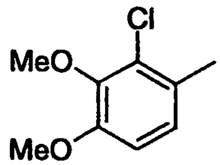
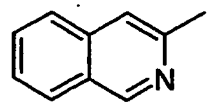
 ;  ;  ;

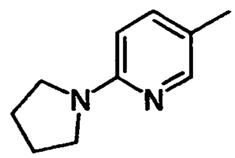
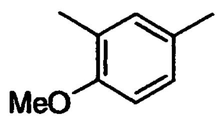
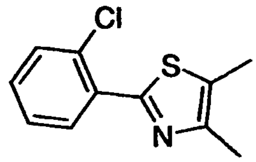
 ;  ;  ;

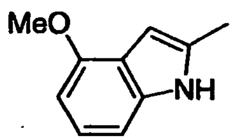
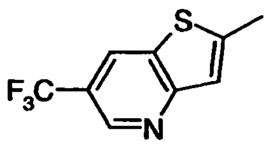
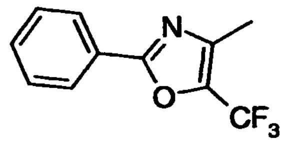
 ;  ;  ;

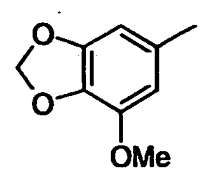
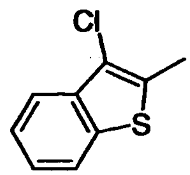
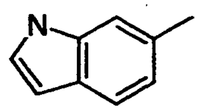
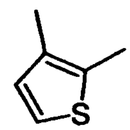
 ;  ;  ;

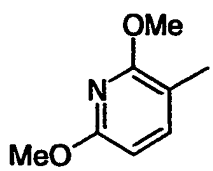
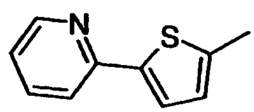
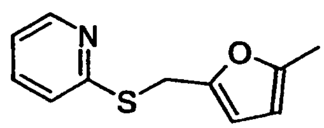

Cl
O
;

NH
;

MeO
NH
;

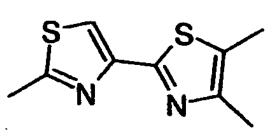
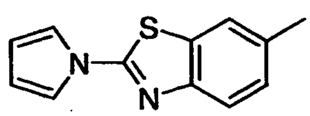
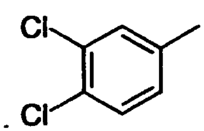

O
;

Cl
MeO
MeO
;

N
;

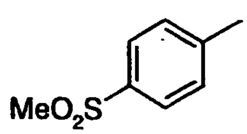
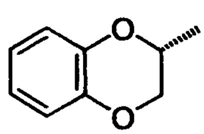
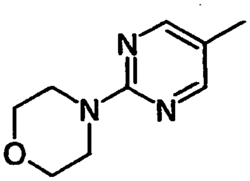

N
N
;

MeO
;

Cl
S
N
;

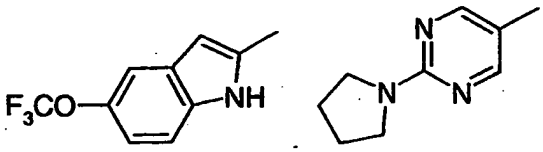

MeO
NH
;

S
F3C
N
;

N
O
CF3
;

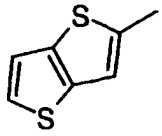
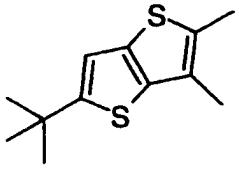
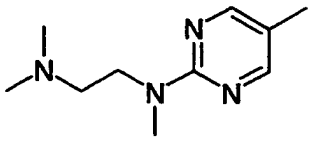
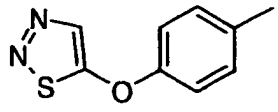
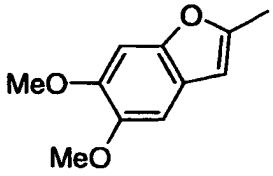
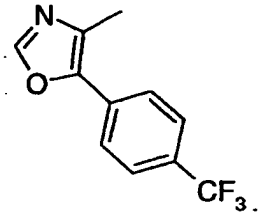
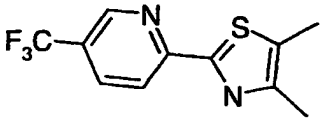
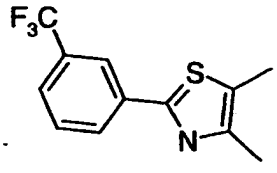
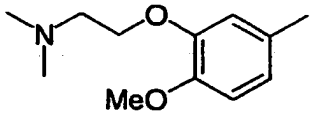
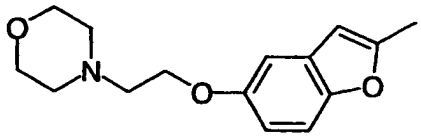
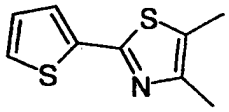
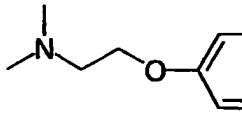
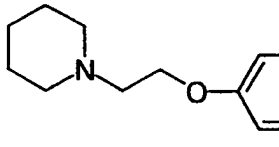
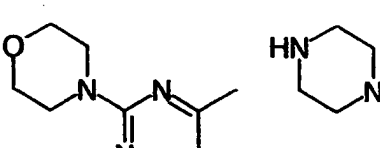
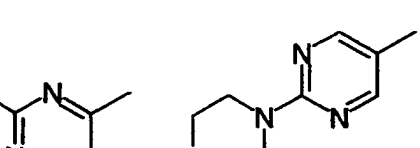
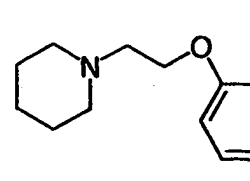
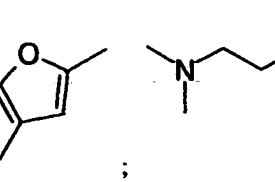
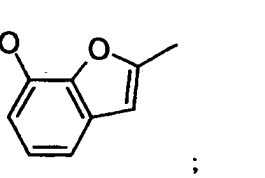

O
O
OMe
;

Cl
S
;

N
;

S
;

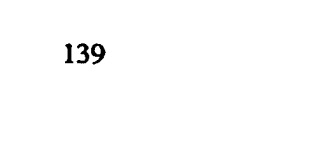

OMe
N
MeO
;

N
S
;

N
S
O
;

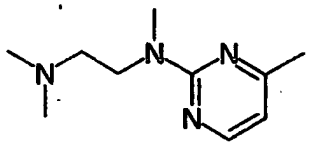
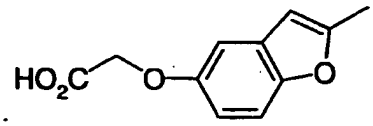

S
N
S
N
;

N
S
N
;

Cl
Cl
;

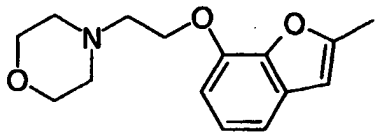
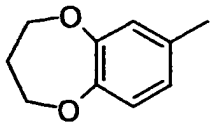

MeO2S
;

O
O
;

N
N
N
O
;

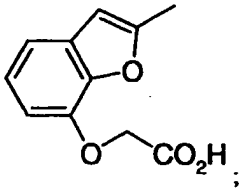
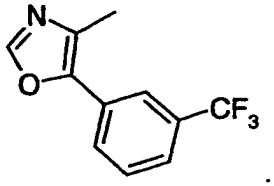
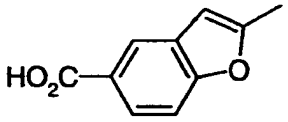

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;


;

;


;

;


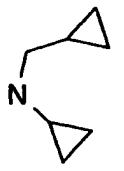
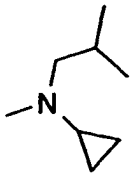
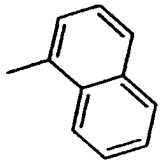
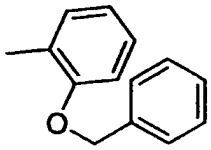
;and

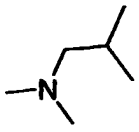
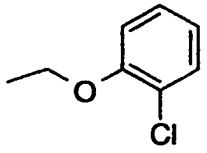
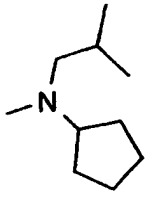
R^{16} is independently selected from the group consisiting of:

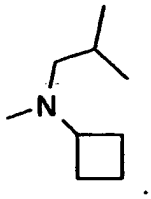

; and

.

L is independently selected from the group consisting of:


;

;

;

;


;

;

;


.

5. A compound of Claim 1 selected from the group consisting of:

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-leucinyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(2 -pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-methylpicolinoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[N-(3,4-difluorobenzoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-(3-propyloxypicolinoyl)-L-leucinyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrazolyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[N-[6-(1-imidazolyl)nicotinoyl]-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-[N-methyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[6-(4-trofluoromethylphenyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[N-(6-methylpicolinoyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide;

N-[N-(5-butyl-2-pyridinylmethoxycarbonyl)-L-leucinyl]-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-[N-(6-phenyldicotinoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

(1S)-N-[4-[1-(N-benzyloxycarbonylamino)-3-methylbutyl]thiazol-2-ylcarbonyl]-N'-[2-(2-chlorophenoxymethyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(6-phenylnicotinoyl)-L-leucinyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide;

N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[N-(5-butylpicolinoyl)-L-β-cyclopropylalanyl]-N'-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[4-(2-pyridinyl)benzoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(5-butylpicolinoyl)-L-leucinyl]-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-imidazolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrazolyl)nicotinoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolyl)nicotinoyl]-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-methylenedioxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-difluorobenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methylimidazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylacetyl)-L-β-cyclopropylalanyl]hydrazide;

N-[N-(benzothiazol-6-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-(N-benzothiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-hydroxymethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-hydroxymethylbenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-(N-benzothiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-indole-2-ylcarbonyl-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-β-*tert*-butylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethoxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-propyloxybenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-(2-pyridinyl)benzoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-(2-pyridinyl)benzoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethylbenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-(N-benzothiazol-6-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-benzothiophen-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyll-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,3-dihydrobenzofuran-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-(N-benzothiophen-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenylimidazol-4-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4,5-trimethoxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-hydroxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-4-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-5-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-(N-benzimidazol-5-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-fluoroindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methyl-2-phenylthiazol-5-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methyl-2-phenyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyquinolin-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[N-(5-chloroindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-benzothiazol-6-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-flurorbenzimidazol-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-quinolin-3-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(7-methoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[N-(5-chlorobenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-trifluoromethoxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(1-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methylindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-(N-benzofuran-2-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[N-(2-chloro-3,4-dimethoxybenzoyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-isoquinolin-3-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-2-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-(N-benzofuran-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[6-(1-pyrrolidinyl)nicotinoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methyl-2-phenylthiazol-5-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(5-chlorobenzofuran-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-(N-benzimidazol-5-ylcarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxyindole-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(5-chloroindole-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxy-3-methylbenzoyl)-L-leucinyl]hydrazide;

N-[N-[2-(2-chlorophenyl)-4-methylthiazol-5-ylcarbonyl]-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyindole-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-trifluoromethyl-4-azabenzothiophen-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-phenyl-5-trifluoromethyloxazol-4-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methoxyquinolin-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methoxy-4,5-methylenedioxybenzoyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-2-ylcarbonyl-L-leucinyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(7-methoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[N-(3-chlorobenzothiophen-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-6-ylcarbonyl-L-leucinyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methylthiophene-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,6-dimethoxynicotinoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-pyridinyl)thiophen-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-mercaptopyridinylmethyl)furan-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-indole-6-ylcarbonyl-L-leucinyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-methylthiazol-4-yl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolyl)benzothiazol-6-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dichlorobenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(4-methanesolfonylbenzoyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2-phenyl-5-trifluoromethyloxazol-4-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[N-[2-(2-chlorophenyl)-4-methylthiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-β-cyclohexylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(6-trifluoromethyl-4-azabenzothiophen-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(2,6-dimethoxynicotinoyl)-L-leucinyl]hydrazide;

(2S)-N-(N-benzodioxan-2-ylcarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(2-pyridinyl)thiophen-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-propionyl-L-leucinyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(4-morpholino)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-methylthiazol-4-yl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolyl)benzothiazol-6-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-trifluoromethoxyindol-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-pyrrolidino)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-(N-butyryl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(3-methylbutyryl)-L-leucinyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]-N'-[N-(3,4-dimethoxybenzoyl)-L-cyclohexylglycinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-thieno[2,3-b]thiophen-2-ylcarbonyl-L-leucinyl)hydrazide;

N-[N-(5-*tert*-butyl-3-methylthieno[2,3-b]thiophen-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-(1,2,3-thiadiazol-5-yloxy)benzoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-(4-triflouormethylphenyl)oxazol-4-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(3-trifluoromethylphenyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(2-thienyl)thiazol-5-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3-[2-(N,N-dimethylamino)ethoxy]-4-methoxybenzoyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(1-piperidinyl)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(N-thieno[2,3-b]thiophen-2-ylcarbonyl-L-β-cyclopropylalanyl)hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[4-methyl-2-(5-trifluoromethylpyridin-2-yl)thiazol-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5,6-dimethoxybenzofuran-2-ylcarbonyl)-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(4-morpholino)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-(1-piperazinyl)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(1-piperidinyl)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]- N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-ylcarbonyl]-L-β-cyclopropylalanyl]hydrazide

N-[N-(5-carboxymethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[7-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[3,4-(1,3-propylenedioxy)benzoyl]-L-leucinyl]hydrazide;

N-[N-(7-carboxymethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-(3-triflouormethylphenyl)oxazol-4-ylcarbonyl]-L-leucinyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-[5-[2-(4-morpholino)ethoxy]benzofuran-2-ylcarbonyl]-L-leucinyl]hydrazide;

N-[N-(5-carboxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide; and

N-[N-(7-carboxymethoxybenzofuran-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide.

6. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.

7. A pharmaceutical composition comprising a compound according to Claim 5 and a pharmaceutically acceptable carrier, diluent or excipient.

8. A method of inhibiting a protease selected from the group consisting of a cysteine protease and a serine protease, comprising administering to a patient in need thereof an effective amount of a compound according to Claim 1.

9. A method of inhibiting a protease selected from the group consisting of a cysteine protease and a serine protease, comprising administering to a patient in need thereof an effective amount of a compound according to Claim 5.

10. A method according to Claim 8 wherein said protease is a cysteine protease.

11. A method according to Claim 9 wherein said protease is a cysteine protease.

12. A method according to Claim 10 wherein said cysteine protease is cathepsin K.

13. A method according to Claim 11 wherein said cysteine protease is cathepsin K.

14. A method of treating a disease characterized by bone loss comprising inhibiting said bone loss by administering to a patient in need thereof an effective amount of a compound according to Claim 1.

15. A method according to Claim 14 wherein said disease is osteoporosis.

16. A method according to Claim 14 wherein said disease is periodontitis.

17. A method according to Claim 14 wherein said disease is gingivitis.

18. A method of treating a disease characterized by excessive cartilage or matrix degradation comprising inhibiting said excessive cartilage or matrix degradation by administering to a patient in need thereof an effective amount of a compound according to Claim 1.

19. A method according to Claim 18 wherein said disease is osteoarthritis.

20. A method according to Claim 18 wherein said disease is rheumatoid arthritis.

21. A method of treating a disease characterized by bone loss comprising inhibiting said bone loss by administering to a patient in need thereof an effective amount of a compound according to Claim 5.

22. A method according to Claim 21 wherein said disease is osteoporosis.

23. A method according to Claim 21 wherein said disease is periodontitis.

24. A method according to Claim 21 wherein said disease is gingivitis.

25. A method of treating a disease characterized by excessive cartilage or matrix degradation comprising inhibiting said excessive cartilage or matrix degradation by administering to a patient in need thereof an effective amount of a compound according to Claim 5.

26. A method according to Claim 25 wherein said disease is osteoarthritis.

27. A method according to Claim 25 wherein said disease is rheumatoid arthritis.

28. A compound selected from the group consisting of:

3-(6-methyl)pyridylcarbinol;

L-β-*tert*-butylalanine methyl ester;

β-isocyanato-L-β-*tert*-butylalanine methyl ester;

N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

N-cyclopropylmethylcyclopropylamine;

N-benzoyl-N'-cyclopropyl-N'-cyclopropylmethylthiourea;

N-cyclopropyl-N-cyclopropylmethylthiourea;

ethyl 2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazole-4-carboxylate;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

ethyl 6-phenylnicotinate;

6-phenylnicotinic acid;

N-cyclopropyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclopropyl-N'-(2-methylpropyl)thiourea;

N-cyclopropyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

4-carbomethoxyphenylboronic acid;

methyl 4-(2-pyridinyl)benzoate;

4-(2-pyridinyl)benzoic acid;

ethyl 2-(1-naphthyl)thiazole-4-carboxylate;

2-(1-naphthyl)thiazole-4-ylcarbonylhydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanine;

N-(N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-*tert*-butylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

2-(2-chlorophenoxymethyl)thiazol-4-ylcarbonylhydrazide;

N-cyclopentyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclopentyl-N'-(2-methylpropyl)thiourea;

N-cyclopentyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

(S)-2-*tert*-butoxycarbonylaminopent-4-enoic acid;

N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine methyl ester;

N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-cyclopropylalanyl)-N'-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-cyclopropylalanyl)hydrazide;

N-cyclobutyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclobutyl-N'-(2-methylpropyl)thiourea;

N-cyclobutyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;
N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;
L-β-cyclopropylalanine methyl ester;
β-isocyanato-L-β-cyclopropylalanine methyl ester;
N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanine methyl ester;
N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanine;
N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;
N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;
N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;
N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-cyclopropylalanyl)hydrazide;
N-(N-*tert*-butoxycarbonyl-L-β-cyclohexylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;
N-(L-β-cyclohexylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;
ethyl 2-(4-morpholino)pyrimidine-5-carboxylate;
2-(4-morpholino)pyrimidine-5-carboxylic acid;
ethyl 2-(1-pyrrolidino)pyrimidine-5-carboxylate;
2-(1-pyrrolidino)pyrimidine-5-carboxylic acid:
N-(N-*tert*-butoxycarbonyl-L-β-cyclohexylglycinyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;
N-(L-β- cyclohexylglycinyl)-N'-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]hydrazide;
ethyl 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylate;
2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylic acid;
ethyl 5-hydroxybenzofuran-2-carboxylate;
ethyl 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylate;
5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid;
ethyl 5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylate;
5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid;

ethyl 5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylate;

5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid;

ethyl 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylate;

2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylic acid;

N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylate;

2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylic acid;

N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-5-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 7-hydroxybenzofuran-2-carboxylate;

ethyl 7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylate;

7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid;

ethyl 7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylate;

7-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid;

ethyl 7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylate;

7-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid;

ethyl 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-4-carboxylate;

2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-4-carboxylic acid;

2-(1-naphthyl)thiazole-4-carboxylic acid;

benzyl 5-hydroxybenzofuran-2-carboxylate;

benzyl 5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylate;

5-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid;

N-[N-(5-*tert*-butoxycarbonylmethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 7-[2-(1-morpholino)ethoxy]benzofuran-2-carboxylate;

7-[2-(1-morpholino)ethoxy]benzofuran-2-carboxylic acid;

benzyl 7-hydroxybenzofuran-2-carboxylate;

benzyl 7-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylate;

7-*tert*-butoxycarbonylmethoxybenzofuran-2-carboxylic acid;

N-[N-(7-*tert*-butoxycarbonylmethoxybenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

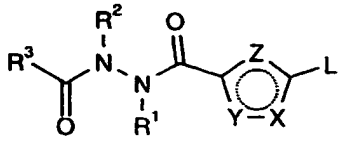
benzyl 5-methoxycarbonylbenzofuran-2-carboxylate;

5-methoxycarbonylbenzofuran-2-carboxylic acid;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-[N-(5-methoxycarbonylbenzofuran-2-ylcarbonyl)-L-β-cyclopropylalanyl]hydrazide; and

N-[N-(7-*tert*-butoxycarbonylmethoxybenzofuran-2-ylcarbonyl)-L-leucinyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide.

29. A process of making a compound of Formula I:



I

wherein:

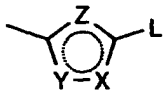
L is selected from the group consisting of:C_{2-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $CH(R^4)NR^5R^6$, $CH(R^4)Ar$, $CH(R^4)OAr'$, and NR^4R^7;

X, Y, Z are independently selected from the group consisting of: N, O, S and CR^{10}, provided that at least two of X, Y and Z are heteroatoms and at least one of X, Y and Z is N, or one of X, Y and Z is C=N, C=C or N=N and the other two are CR^{10} or N, provided that X, Y and Z together comprise at least two N;

– indicates a single or double bond in the five-membered heterocycle;

R', R^1, R^2, R^5, R^{10}, R^{12}, R^{16} and R^{17} are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^3 is selected from the group consisting of: C_{3-6}alkyl, Ar, Het, $CH(R^{11})Ar$, $CH(R^{11})OAr$, $NR^{11}R^{12}$, $CH(R^{11})NR^{12}R^{13}$; and



;

R^4, R^{11}, and R^{15} are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-11}cycloalkyl-C_{0-6}-alkyl, Ar-C_{0-6}alkyl, Ar-C_{2-}

$_6$alkenyl, Ar-C_{2-6}alkynyl, Het-C_{0-6}alkyl, Het-C_{2-6}alkenyl, Het-C_{2-6}alkynyl, C_{1-6}alkyl, optionally substituted by OR^8, SR^8, NR^8R^9, $N(R')CO_2R'$, CO_2R', $CONR^{10}R^{11}$, and $N(C=NH)NH_2$;

R^6 and R^{13} are independently selected from the group consisting of: R^{14}, $R^{14}C(O)$, $R^{14}C(S)$, $R^{14}OC(O)$, and $R^{14}OC(O)NR^9CH(R^{15})(CO)$;

R^7 is selected from the group consisting of: C_{1-6}alkyl, C_{1-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}-alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^4 and R^7 may be combined to form a 3-7 membered monocyclic or 7-10-membered bicyclic carbocyclic or heterocyclic ring, optionally substituted with 1-4 of C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkoxy, Ar-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}NR^8R^9$, $O(CH_2)_{1-6}NR^8R^9$;

$R^8$and R^9 are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, and $R^{16}R^{17}NC_{2-6}$alkyl;

R^{14} is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

comprising the step of converting a compound selected from the group consisting of:

3-(6-methyl)pyridylcarbinol;

L-β-*tert*-butylalanine methyl ester;

β-isocyanato-L-β-*tert*-butylalanine methyl ester;

N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(6-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

N-cyclopropylmethylcyclopropylamine;

N-benzoyl-N'-cyclopropyl-N'-cyclopropylmethylthiourea;

N-cyclopropyl-N-cyclopropylmethylthiourea;

ethyl 2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazole-4-carboxylate;

N-[2-(N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

ethyl 6-phenylnicotinate;

6-phenylnicotinic acid;

N-cyclopropyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclopropyl-N'-(2-methylpropyl)thiourea;

N-cyclopropyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(2-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

4-carbomethoxyphenylboronic acid;

methyl 4-(2-pyridinyl)benzoate;

4-(2-pyridinyl)benzoic acid;

ethyl 2-(1-naphthyl)thiazole-4-carboxylate;

2-(1-naphthyl)thiazole-4-ylcarbonylhydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-(L-leucinyl)-N'-[2-(1-naphthyl)thiazol-4-ylcarbonyl]hydrazide;

N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanine;

N-(N-*tert*-butoxycarbonyl-L-β-*tert*-butylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-*tert*-butylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine methyl ester;

N-(2-methyl-3-pyridinylmethoxycarbonyl)-L-β-*tert*-butylalanine;

2-(2-chlorophenoxymethyl)thiazol-4-ylcarbonylhydrazide;

N-cyclopentyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclopentyl-N'-(2-methylpropyl)thiourea;

N-cyclopentyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

(S)-2-*tert*-butoxycarbonylaminopent-4-enoic acid;

N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine methyl ester;

N-*tert*-butoxycarbonyl-L-β-cyclopropylalanine;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-cyclopropylalanyl)-N'-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-cyclopropylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclopentyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-cyclopropylalanyl)hydrazide;

N-cyclobutyl-N-(2-methylpropyl)amine;

N-benzoyl-N'-cyclobutyl-N'-(2-methylpropyl)thiourea;

N-cyclobutyl-N-(2-methylpropyl)thiourea;

ethyl 2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazole-4-carboxylate;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

L-β-cyclopropylalanine methyl ester;

β-isocyanato-L-β-cyclopropylalanine methyl ester;

N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanine methyl ester;

N-(2-pyridinylmethoxycarbonyl)-L-β-cyclopropylalanine;

N-(N-*tert*-butoxycarbonyl-L-leucinyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-leucinyl)hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclopropylalanyl)-N'-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-[2-[N-cyclobutyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]-N'-(L-β-cyclopropylalanyl)hydrazide;

N-(N-*tert*-butoxycarbonyl-L-β-cyclohexylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

N-(L-β-cyclohexylalanyl)-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 2-(4-morpholino)pyrimidine-5-carboxylate;

2-(4-morpholino)pyrimidine-5-carboxylic acid;

ethyl 2-(1-pyrrolidino)pyrimidine-5-carboxylate;

2-(1-pyrrolidino)pyrimidine-5-carboxylic acid;

N-(N-*tert*-butoxycarbonyl-L-β-cyclohexylglycinyl)-N'-[2-)N-cyclopropyl-N-cyclopropylmethylamino)thiazol-4-ylcarbonyl]hydrazide;

N-(L-β- cyclohexylglycinyl)-N'-[2-(N-cyclopropyl-N-cyclopropylmenthylamino)thiazol-4-ylcarbonyl]hydrazide;

ethyl 2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylate;

2-[N-[2-(N,N-dimethylamino)ethyl]-N-methylamino]pyrimidine-5-carboxylic acid;

ethyl 5-hydroxybenzofuran-2-carboxylate;

ethyl 5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylate;

5-[2-(4-morpholino)ethoxy]benzofuran-2-carboxylic acid;

ethyl 5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylate;

5-[2-(N,N-dimethylamino)ethoxy]benzofuran-2-carboxylic acid;

ethyl 5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylate;

5-[2-(1-piperidinyl)ethoxy]benzofuran-2-carboxylic acid;

ethyl 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylate;

2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-4-carboxylic acid;

N-[N-[2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidin-4-ylcarbonyl]-L-β-cyclopropylalanyl]-N'-[2-[N-cyclopropyl-N-(2-methylpropyl)amino]thiazol-4-ylcarbonyl]hydrazide;

ethyl 2-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrimidine-5-carboxylate;